Measurement of Meperidine-Induced Respiratory Depression Using a New Non-Invasive Technique

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Summary

Inductive plethysmography was used to assess the magnitude and duration of respiratory depression caused by doses of meperidine commonly administered during dental intravenous sedation. Minute volume measurements exhibited a high degree of accuracy when compared to simultaneous spirometry. Intravenously administered meperidine 25 mg/70 kg and 50 mg/70 kg both caused a significant shift to the right in their respective ventilatory-pCO2 response curves. The magnitude and duration of this respiratory depression was dose related. Even relatively low doses of meperidine used in dental intravenous sedation cause respiratory depression.

Introduction

Respiratory depression is the most hazardous side effect of intravenous sedation regimens. While conscious sedation is very popular among oral surgeons1 and has been utilized by other dental practitioners,2 the dilemma still exists of recognizing respiratory depression before there are severe clinical manifestations. Spirometry and other techniques which directly measure air flow or volume are impractical when the oral cavity is the surgical field. The respiratory inductive plethysmograph (RIP) is a noninvasive device that measures tidal volume through coils placed around the rib cage and abdomen. This technique reportedly exhibits a high degree of accuracy when compared to simultaneously measured spirometric volumes.4,7 The ability of the RIP to monitor respiration without the use of a mouthpiece makes it particularly attractive in monitoring patients under dental sedation.

Prior to monitoring actual dental patients with this device, it was necessary to evaluate the plethysmograph’s ability to record drug-induced respiratory changes in normal volunteers. Meperidine, the most widely used narcotic in dental intravenous sedation,1 was chosen as the prototype agent to initially evaluate this system. Meperidine’s ability to depress respiration had been demonstrated in a number of studies.8-10 However, the doses of meperidine utilized in these studies were far greater than those routinely administered for dental sedation.

Studies within the dental literature have only reported drug effects on individual respiratory parameters while breathing room air.10-13 Although useful information has been gained from these studies, we felt it important to more adequately assess the effects of sedative dosages of meperidine upon central respiratory drive. The classical technique with which the respiratory effects of drugs have been quantified is to chemically stimulate respiratory drive with increasing concentrations of inhaled CO2.6,14-17 In this way both control and postdrug measurements can be compared at the same stimulus levels. The purpose of this study was to compare the accuracy and sensitivity of plethysmography with that of traditional pneumotach spirometry and to assess the magnitude and duration of respiratory depression produced by doses of meperidine commonly administered in dental practice.
Methods

This investigation was carried out on 8 healthy volunteers ranging from 23 to 28 years old. Seven of the eight subjects were male. Patient weights ranged from 135 (61.2 kg) to 192 pounds (87.1 kg). The experimental protocol and possible risks involved were explained to subjects prior to their participation in the study. Each subject signed a consent form which along with the protocol had been previously approved by the New Jersey Dental School Human Use Committee.

All trials were conducted in the Oral Surgery Clinic of UMDNJ-New Jersey Dental School. A special surgical/anesthesia suite was utilized for the duration of the study. Emergency equipment included positive pressure oxygen and naloxone (Narcan) to reverse any untoward drug effects. Patients were seated in a reclining dental chair during the experiment. All respiratory monitoring equipment was placed out of the direct view of the patient.

A three-way complete crossover design was utilized, in which each subject received all three treatments with a minimum washout period of 5 days between treatments. The possible study treatments were intravenous saline placebo, meperidine 25 mg/70 kg, and meperidine 50 mg/70 kg. Medication was administered over two minutes through a 21 gauge venous catheter in the left antecubital vein. An investigator not directly involved with data collection or analysis administered the drug. All other investigators and patients were unaware of which study medication was being administered.

Prior to each experimental session the pneumotach spirometer-integrator system (Hewlett Packard 8815A, Paramus, N.J.) was calibrated using a one liter air syringe. In use, the 8815A receives an input signal proportional to respiratory air flow. The signal is processed by tidal and minute integrators, resulting in a recording of tidal or minute volume in liters. At the beginning of each experimental session, vital signs were recorded and the belts of the respiratory inductive plethysmograph were placed. The thoracic belt was placed just below the axilla and the abdominal belt was placed at or slightly below the umbilicus. The belts were maintained in position by adhesive tape and an elastic meshwork applied over the belts. Care was taken not to fold or twist the belts and their final position was adjusted after the retainer was in place.

The respiratory inductive plethysmograph (Respirtrace®, Ambulatory Monitoring Inc., White Plains, N.Y.) was then calibrated against the pneumotach spirometer using the graphic method of least squares described by Watson et al. Briefly, this involves the collection of pneumotach volume signals and RIP rib cage and abdominal signals in standing and supine positions. A best-fit straight line was constructed with the RIP abdominal signal/pneumotach volume signal representing the X axis and the RIP thoracic signal/pneumotach volume signal representing the Y axis. The reciprocal of each intercept represented the abdominal and thoracic gains which were then entered into the calibrating component of the plethysmograph. The initial calibration was validated if the sum tidal volume signals of the RIP were within 10% of that simultaneously recorded by the pneumotach spirometer. The calibration procedure was repeated if the above criteria were not met.

Throughout this study, tidal volume and respiratory rate were monitored simultaneously by the RIP and pneumotach spirometer; and minute volume was later calculated. End tidal pCO₂ was monitored continuously using an infrared carbon dioxide analyzer (Hewlett Packard Capnograph 47210A) attached to the expiratory end of the pneumotach mouthpiece assembly. Increasing concentrations of carbon dioxide were delivered from separate reservoir bags through the inspiratory portion of the mouthpiece assembly. Patients successively breathed room air, 2.5% CO₂, 5.0% CO₂ and 7.5% CO₂ each in 30% oxygen, for four minutes at each concentration. Respiratory data were analyzed during the last minute of each carbon dioxide challenge at the baseline (pre-drug) session, then immediately, 30 minutes and 60 minutes postdrug infusion.

The inspiratory tidal volume signals from the RIP and pneumotach spirometer were used to calculate minute ventilation at the various data collecting periods. The percent difference in minute ventilation (MV) obtained from the RIP and the pneumotach spirometer at the various data collecting periods was calculated using the formula:

\[
\text{% Difference} = \frac{(\text{Pneumotach} \ MV - \text{RIP} \ MV)}{\text{RIP} \ MV} \times 100
\]

Minute ventilation-pCO₂ response curves were constructed for each treatment group. The displacement from baseline was calculated at the 16 liter intercept since this fell approximately halfway up the baseline respiratory response curves. One way analysis of variance was used to test for differences among treatments. If the ANOVA was significant at \( p < 0.05 \), pairwise differences were further analyzed using Duncan’s multiple means test.

Results

Minute ventilation values were calculated for both the respiratory inductive plethysmograph and the pneumotach spirometer during a total of 384 data collecting periods. The overall accuracy of the RIP compared to the pneumotach differed by only ± 8.91 percent. The accuracy of the RIP remained fairly constant over time and with increasing minute volume during carbon dioxide inhalation. These results are summarized in Table 1. Figure 1 illustrates the accuracy of the RIP compared to the pneumotach during a baseline carbon dioxide ramp. Each point
TABLE 1. Percent Difference of Respiratory Inductive Plethysmograph Minute Ventilation Values from that of Pneumotach Spirometer

<table>
<thead>
<tr>
<th>Data collecting periods</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.08±(0.72)</td>
</tr>
<tr>
<td>Immediate postdrug</td>
<td>8.81±(0.69)</td>
</tr>
<tr>
<td>30 Minutes postdrug</td>
<td>8.89±(0.72)</td>
</tr>
<tr>
<td>60 Minutes postdrug</td>
<td>9.53±(0.81)</td>
</tr>
<tr>
<td>Room air</td>
<td>7.12±(0.62)</td>
</tr>
<tr>
<td>2.5% Carbon dioxide</td>
<td>8.78±(0.69)</td>
</tr>
<tr>
<td>5.0% Carbon dioxide</td>
<td>9.43±(0.76)</td>
</tr>
<tr>
<td>7.5% Carbon dioxide</td>
<td>10.24±(0.63)</td>
</tr>
<tr>
<td>Overall (n=384)</td>
<td>8.91±(0.37)</td>
</tr>
</tbody>
</table>

n = 96 observations at each period. Data expressed as mean C (SEM).

Fig. 1—Ventilatory-end-tidal pCO2 baseline response curves of a single patient comparing Respitrace (RIP) to pneumotach spirometer.

Fig. 2—Effect of saline placebo, meperidine 25 mg/70 kg, and meperidine 50 mg/70 kg on baseline respiratory response curves during the inhalation of room air, 2.5, 5.0, and 7.5 percent CO2 (immediately postdrug).

Fig. 3—Effect of saline placebo, meperidine 25 mg/70 kg and meperidine 50 mg/70 kg on baseline respiratory response curves during the inhalation of room air, 2.5, 5.0, and 7.5 percent CO2 (30 minutes postdrug).

represents the minute ventilation and end-tidal pCO2 recorded at each carbon dioxide concentration (room air, 2.5%, 5.0%, and 7.5%). It should be noted that differences in minute ventilation between the two systems reflected differences in tidal volume since respiratory rate always coincided.

Figures 2, 3, and 4 represent the overall eight patient regression ventilatory-pCO2 response curves at baseline (control), then immediately, 30 and 60 minutes postdrug. Each curve was constructed from four points representing the mean values of minute ventilation and end-tidal pCO2 obtained during the last minute of breathing each gas mixture. Correlation coefficients for these curves were all greater than +0.98. Only minute ventilation values measured by the RIP are presented since they so closely followed that of the pneumotach spirometer. Respiratory depression was determined by the direction and magnitude of the shift in the postdrug respiratory response curves from baseline curves. A significant shift to the right compared to placebo is indicative of respiratory depression. The minute ventilation pCO2 response curves for the 25 mg and 50 mg meperidine treatments were displaced 5.97 and 10.06 mmHg to the right, respectively, immediately postdrug (Fig. 2). Both treatments depressed respiration significantly compared to placebo (p<.05). There was a slight increase in the overall respiratory response shown by a slight shift to the left (−1.80 mmHg) after the placebo treatment. At 30 minutes (Fig. 3) and 60
Respiratory monitoring by mouth during dental intravenous sedation is not feasible because the oral cavity is the surgical field. While a disadvantage of the RIP is the time required for calibration, clinicians could observe patients' respiratory tracings prior to and after drug administration without calibrating the system. Although the signals would have no quantitative values, large decreases in tidal volume signals or prolonged apneic periods would indicate that the patient may be excessively depressed. Appropriate action could be taken before overt clinical signs of depressed respiration occurred. The RIP may be especially useful in pedodontic patients who are frequently administered multiple agents that may depress respiration. Many of these patients are wearing a rubber dam and are restrained using a papoose board, making it difficult to visualize abdominal and chest movements. The inability of the clinician to promptly recognize and treat respiratory depression can have devastating effects.20, 21

One interesting observation was that respiratory rate was never significantly altered after drug administration, even at peak drug effect. It was the tidal volume component of minute ventilation that became significantly depressed. The possible significance of this is that overt respiratory depression in the dental intravenous sedation patient may be initially manifested in decreased respiratory depth with respiratory rate remaining unchanged. Therefore, simply observing the frequency of patient breathing may not adequately assess the situation.

For many years clinical pharmacologists have shown that the respiratory response to inhaled carbon dioxide is a useful method for determining the respiratory depressant effects of anesthetic and analgesic agents. In the present study this methodology was used to compare the respiratory effects of two intravenous doses of meperidine with that of saline placebo. While other studies have demonstrated the respiratory depressant effects of meperidine during CO2 inhalation,8, 9 the present study showed that even clinically relevant dosages in dentistry depress respiratory drive significantly. While none of the normal volunteers exhibited clinically overt respiratory depression, these results have clinical importance in high-risk patients with pre-

**TABLE 2.** The Effect of Placebo, Meperidine 25 mg/70 kg, and Meperidine 50 mg/70 kg on the Displacement of CO2 Response Curves at a Minute Ventilation of 16 Liters

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Immediately Post Drug</th>
<th>30 Minutes Post Drug</th>
<th>60 Minutes Post Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline placebo</td>
<td>-1.80±1.10</td>
<td>-1.40±1.79</td>
<td>-1.42±1.73</td>
</tr>
<tr>
<td>Meperidine 25 mg</td>
<td>+5.97±1.36</td>
<td>+2.69±1.61</td>
<td>+2.07±0.89</td>
</tr>
<tr>
<td>Meperidine 50 mg</td>
<td>+10.06±2.64</td>
<td>+6.57±1.68</td>
<td>+4.17±1.80</td>
</tr>
</tbody>
</table>

n = 8 Data expressed as mean ± SEM

*significantly different from placebo (p < .05).
existing pulmonary disease and in some healthy individuals who are overly sensitive to the drug's effect. The ability of other centrally acting agents, commonly administered in combination with meperidine, to potentiate the narcotic's respiratory depressant effects should be evaluated in future studies.

References