CONTROL OF BREATHING AFTER FENTANYL AND INNOVAR ANAESTHESIA†

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SUMMARY

Ventilation ($V_t$), end-tidal ($P_{CO_2}$), mixed venous ($P_{CVCO_2}$) and the ventilatory response to carbon dioxide were measured before surgery, and during the first 4 h of recovery in 18 adult patients who underwent elective limb surgery under fentanyl or Innovar anaesthesia. End-tidal and mixed venous $P_{CO_2}$ were increased significantly in the first 150 min after the last dose of drug ($P < 0.001$, $P < 0.01$), but had returned to control values by 4 h. Ventilation and ventilatory response to carbon dioxide were significantly depressed in all patients ($P < 0.001$), but returned to near control values at 4 h. Fentanyl and Innovar anaesthesia displaced the carbon dioxide response to the right, but no correlation was found between either the magnitude of the displacement of the response curve or the alteration in slope and the control values. This suggests that patients with a low value of $V_t/P_{CO_2}$ are not more susceptible to the ventilatory depressant action of narcotic anaesthetics. Recovery of ventilatory responsiveness towards normal during the 4 h after anaesthesia, occurred in a graded and progressive manner; there was no evidence of a biphasic pattern of recovery.

Although Lambertsen (1960) postulated that patients with a low intrinsic ventilatory sensitivity to carbon dioxide might be more susceptible to the depressant action of narcotic drugs, recent studies in volunteer subjects have not confirmed this prediction (Rigg, 1978). However, this concept has not been studied in patients undergoing surgery and anaesthesia, although Becker and colleagues (1976) suggested that a biphasic pattern of recovery of the ventilatory response to carbon dioxide characterized the recovery of ventilatory control in patients following anaesthesia with fentanyl and Innovar.

Accordingly, the present study was designed to examine two questions: first, the relationship of the intrinsic ventilatory response to carbon dioxide to changes in ventilation and carbon dioxide responsiveness during recovery from anaesthesia with either fentanyl/nitrous oxide or Innovar/nitrous oxide; and second, the nature of the biphasic pattern of the ventilatory depression which may occur during recovery from fentanyl/nitrous oxide or Innovar/nitrous oxide anaesthesia.

PATIENTS AND METHODS

**Principle**

Ventilation ($V_t$), end-tidal $P_{CO_2}$ ($P_{ECO_2}$), mixed venous $P_{CO_2}$ ($P_{CVCO_2}$) and the ventilatory response to carbon dioxide ($V_t/P_{CO_2}$) were measured before surgery, and at intervals during the period after operation, in patients having peripheral surgical procedures under either fentanyl/nitrous oxide or Innovar/nitrous oxide anaesthesia.

**Subjects**

Eighteen patients, aged between 19 and 60 yr, and in A.S.A. categories I or II, were studied. All patients underwent elective lower limb surgery and each gave informed consent to the study according to the procedure approved by the McMaster University Ethics Committee.

**Equipment**

Ventilation was measured with a Parkinson–Cowan CD 4 dry gas meter precise to ± 2%. Carbon dioxide was measured with a Godart infra-red analyser, with a response time of 0.1 s and a precision of 0.2%, over the range of 0–10%. The analyser was calibrated with three gas mixtures of carbon dioxide, 40% oxygen and balance nitrogen, each of which had been analysed previously with the Lloyd Haldane apparatus. A continuous record of $P_{CO_2}$ and $V_t$ was obtained with an Astromed pen recor-
Ventilatory responses to carbon dioxide (\(V_I/PCO_2\)) were measured by the method of Read using criteria of validity described previously (Read, 1967; Rigg, Reubuck and Campbell, 1974). Oxygenated \(PvCO_2\) was obtained by the equilibrium rebreathing method, before each determination of the carbon dioxide response (Hackney, Sears and Collier, 1958).

**Experimental programme**

Patients were allocated sequentially to two groups. Nine received fentanyl (group I) and nine Innovar (group II) as the test drug.

Group I patients were premedicated with fentanyl 1.5 \(\mu\)g kg\(^{-1}\) i.m. This was followed approximately 1 h later by fentanyl 4.5 \(\mu\)g kg\(^{-1}\) at the induction of anaesthesia. Incremental doses of fentanyl 0.75 \(\mu\)g kg\(^{-1}\) were administered i.v. as indicated by movement of the patient during surgery. Innovar was administered to the second group in a similar manner. All patients received thiopentone 4 mg kg\(^{-1}\) and suxamethonium 1 mg kg\(^{-1}\) at the induction of anaesthesia. Tracheal intubation was performed and ventilation of the lungs assisted by hand until spontaneous breathing resumed.

There were no significant differences between the two groups in respect of age, sex distribution, weight, height, vital capacity, duration of surgery (group 1, 53 min ± 6; group 2, 59 min ± 10) and total dose of fentanyl or Innovar administered (group 1, 454 \(\mu\)g ± 27; group 2, 436 \(\mu\)g ± 34).

Immediately following surgery patients were taken to a quiet room adjacent to the recovery room and the studies undertaken. Measurements of \(V_I\), \(P^C_{O_2}\), \(PvCO_2\) and \(\Delta V_I/\Delta PCO_2\) were performed at 15, 45, and 90 min after the end of anaesthesia, and at 240 min after the last dose of the test drug.

**Analysis of data**

In order to compare the position of the response curves before and after anaesthesia, the greatest \(PCO_2\) value common (iso-\(PCO_2\)) to control and post-anaesthetic response was chosen for each subject. These iso-\(PCO_2\) points were used to compare ventilation among the several responses of an individual patient, as a measure of the position of the response curve (fig. 1). This procedure was adopted because subjects rebreathed over widely differing carbon dioxide tensions. These iso-\(PCO_2\) ventilation variables were actual measurements obtained during rebreathing. Thus, errors from extrapolation of the position of the response curve which would be inevitable if a single \(PCO_2\) value was used for all runs in all subjects, were avoided (Rigg et al., 1977).

The slopes of all response curves were calculated by least-squares regression. The degree of ventilatory depression in the recovery period was expressed as a percentage of control. Paired \(t\) tests were used to determine the significance of changes induced by the drugs.

**RESULTS**

Profound depression of ventilation and of the ventilatory response to carbon dioxide was seen in all patients following both fentanyl and Innovar anaesthesia (table I, figs 2 and 3).

End-tidal \(PCO_2\) and \(PvCO_2\) were increased significantly for up to 150 min after the last dose, but had virtually reattained their control values by 4 h (mean \(P^C_{O_2}\) values ± SEM: control, 37.8 mm Hg ± 1.1; 15 min, 46.3 mm Hg ± 1.0 (\(P < 0.001\)); 240 min, 40.9 mm Hg ± 1.2 (\(P > 0.05\)) (table I).

Progressive recovery of the ventilatory responsiveness towards normal was observed during the 4-h period after anaesthesia (figs 2, 3). There was no evidence of a biphasic pattern in any of the 18 patients studied. The progressive increase was found in terms of both the slope and the position of curve (fig. 1). In all subjects the depression of ventilation was greater with fentanyl than with Innovar, but this difference was not significant. Since this was consistent for all the variables studied, all the results were pooled for the analysis which compared baseline measurements before operation with
FENTANYL, INNOVAR AND CONTROL OF BREATHING

TABLE I. Mean (± SEM) slopes of the relationships between carbon dioxide and ventilation frequency and tidal volume (Δ Vi/Δ Pco2, Δ Vt/Δ Pco2 and Δ Vt/Δ Pco2) and the positions of the response curve (Pl and Vt at iso-Pco2) before and 15, 45 and 90 min after anaesthesia and 240 min after the last dose of fentanyl (A) or Innovar (B) during anaesthesia. See text for detailed explanation of variables.

<table>
<thead>
<tr>
<th>Control</th>
<th>15 min</th>
<th>45 min</th>
<th>90 min</th>
<th>240 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Δ Vi/Δ Pco2 (litre min⁻¹ mm Hg⁻¹)</td>
<td>Mean</td>
<td>2.09</td>
<td>1.84</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.48</td>
<td>0.54</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Δ Vt/Δ Pco2 (litre mm Hg⁻¹)</td>
<td>Mean</td>
<td>0.53</td>
<td>0.44</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.27</td>
<td>0.24</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.02</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vi at iso-Pco2 (litre min⁻¹)</td>
<td>Mean</td>
<td>47.43</td>
<td>70.48</td>
<td>22.51</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>13.77</td>
<td>9.81</td>
<td>9.28</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>f at iso-Pco2 (breath min⁻¹)</td>
<td>Mean</td>
<td>22.58</td>
<td>18.99</td>
<td>14.98</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6.72</td>
<td>3.35</td>
<td>3.48</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vt at iso-Pco2 (litre)</td>
<td>Mean</td>
<td>2.12</td>
<td>2.21</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.65</td>
<td>0.72</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

recovery measurements.

No relationship was demonstrated between the baseline carbon dioxide responses (slope or position) and the magnitude of the change in any ventilatory variable measured during recovery from fentanyl or Innovar anaesthesia (fig. 4, upper and middle panels). This absence of any correlation was confirmed further when corrections were made for differences in lung size (vital capacity) among patients studied (fig. 4, lower panel).

DISCUSSION

These studies confirm several earlier reports that fentanyl and Innovar cause profound and prolonged depression of breathing in the period after operation (Harper et al., 1976; Vejlsted, Hansen and Jacobsen, 1977). In addition these studies in patients confirm our earlier observations in volunteer adults that the magnitude of the depression of ventilation is not increased in subjects in whom intrinsic ventilatory sensitivity is low (Rigg and Goldsmith, 1976; Rigg, 1978).

Vital capacity is a recognized determinant of the slope of the ventilatory response to carbon dioxide (Avery et al., 1963; Rebuck et al., 1974; Irsigler, 1976). When the present results were corrected for the size of the lung by expressing the ventilatory variables as a percent of vital capacity, there remained no apparent relationship between control measurements and changes in these variables after...
Fig. 2. Slope of ventilatory response to carbon dioxide, \( \Delta V_l/\Delta P_{CO_2} \) (expressed as % of control values) before and during recovery from fentanyl and Innovar anaesthesia. Each bar is the mean of all results in each group at the time. Ventilation is depressed significantly \((P < 0.001)\) at 45, 90 and 150 min, but not at 240 min.

Fig. 3. Ventilation at iso-P_{CO_2} during rebreathing (see text for detailed explanation) (expressed as % of control), before and during recovery from fentanyl and Innovar anaesthesia. Each bar is the mean of all results in each group at that time. Depression of \( V_l \) at iso-P_{CO_2} is very significant at 45, 90 and 150 min after drug administration \((P < 0.001)\).

Becker and colleagues (1976) reported that, following anaesthesia using Innovar or fentanyl, marked respiratory depression was seen immediately after operation with recovery to almost 100% of control within 2 h after the last dose of narcotic. These authors then observed another decrease in ventilatory responsiveness, \( \Delta V_l/\Delta P_{CO_2} \) decreasing to as little as 50% of control at 150 min before a gradual and progressive return towards control at 4 h. They termed this phenomenon the "biphasic" pattern of recovery of ventilatory response to carbon dioxide.

Fig. 4 Upper panel: \( \Delta V_l/\Delta P_{CO_2} \), control, plotted against \( \Delta V_l/\Delta P_{CO_2} \) at 15 min after beginning of recovery. Middle panel iso-P_{CO_2} ventilation during rebreathing, control, plotted against iso-P_{CO_2} ventilation during rebreathing at 15 min after beginning of recovery. Lower panel: \( \Delta V_l/\Delta P_{CO_2} \), control, plotted against \( \Delta V_l/\Delta P_{CO_2} \), 15 min after beginning of recovery, both variables expressed as per cent of VC. In each panel the dashed line is the line of identity.
dioxide after fentanyl and Innovar anaesthesia.

The present results are at variance with those of Becker and co-workers (1976), since all of the patients in the present investigation showed a progressive and relatively constant rate of recovery of their ventilatory responsiveness towards normal. Hug and McClain (1980) in a similar study also reported a progressive recovery of ventilatory responsiveness following narcotic anaesthesia supplemented with enflurane and nitrous oxide in oxygen.

How can these apparently conflicting observations be reconciled? One possible explanation is based upon observations on the pharmacokinetics of fentanyl (Stoeckel, Hengstmann and Schuttler, 1979). These investigators demonstrated small increases in plasma fentanyl concentrations during the elimination phase, which they attributed to entero-systemic recirculation. They postulated that these increases reflected parallel changes in the brain and could account for the biphasic pattern of recovery of ventilatory responsiveness.

Alternatively, the difference between the study of Becker and colleagues (1976) and the present investigation may have a physiological rather than a pharmacological basis. There are two reasons for this. First, the magnitude of the small increase in plasma fentanyl concentration reported during the elimination phase in pharmacokinetic studies is small (less than 5% of the injected dose), transient, and has only been reported at plasma fentanyl concentrations substantially less than threshold concentrations for ventilatory depression in anaesthetized dogs (Murphy, Olson and Hug, 1979). More importantly, in the study in which the transient increases in plasma fentanyl concentration were found, there were no reports of any associated changes in ventilation (Stoeckel, Hengstmann and Schuttler, 1979). Second, the study of Becker and co-workers was carried out in the recovery room, where it is common practice for staff to stimulate drowsy patients vigorously during the early part of their recovery. In contrast, the present studies were conducted in a quiet room adjacent to the recovery room, in the presence of only one or two investigators.

At all times in the present study, quiet conditions were maintained. This procedure was deliberately established as part of the programme in view of the known effects of stimulation on the ventilatory response to carbon dioxide (Gautier, 1969; Rigg et al., 1977). Thus, it is possible that the biphasic pattern of recovery (Becker et al., 1976) and the absence of such a pattern in the present study are a consequence of the different laboratory conditions at the time of study.

An important clinical implication of this study is that preoperative determination of ventilatory response to carbon dioxide has no predictive value in assessing susceptibility to post-anaesthetic ventilatory depression. However, since respiratory depression may persist for up to 4 h after these drugs have been given, a clinical evaluation of the adequacy of respiration should always precede further administration of narcotics to patients who have been given fentanyl or Innovar as part of the anaesthetic technique.

ACKNOWLEDGEMENTS

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We thank Liz Inman for expert technical assistance and Jean Legg for preparation of the manuscript.

REFERENCES


TABLE I. Demographic data of patients (mean ± SD). There is no significant difference in any category

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male/Female</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Duration of anaesthesia (min)</th>
<th>Induction dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>30</td>
<td>20/10</td>
<td>36±12.2</td>
<td>72±9.2</td>
<td>65±20.6</td>
<td>14±1.9</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>30</td>
<td>21/9</td>
<td>35±11.8</td>
<td>71±10.9</td>
<td>63±20.1</td>
<td>215±34.3</td>
</tr>
</tbody>
</table>

recorded 1, 2 and 3 min after induction, at 5-min intervals throughout the anaesthetic and 60 min after cessation of anaesthesia. The e.c.g. was monitored throughout the anaesthetic.

At induction, the times to spontaneous closure of the eye, loss of the eyelash reflex, and the onset of apnoea were recorded.

The Mann–Whitney Rank Sum test was used to assess the comparability of the groups. Bartlett's test was used to assess variance homogeneity. To analyse the data, parametric analysis of variance, x²-test and Student's t test were used.

RESULTS

There were 30 patients in each group and no significant differences as regards sex, age, weight and duration of anaesthesia were demonstrated between the groups (table I). No patient was excluded from the study. The mean dose of midazolam was 14 mg (range 11–18.5 mg) and of thiopentone 215 mg (range 150–300 mg) (table II). Seven patients in the midazolam group and five in the thiopentone group did not become apnoeic (this difference was not significant). Baseline cardiovascular indices were similar in the two groups (table III). Immediately before the administration of midazolam mean (+ SEM) systolic arterial pressure was 118.5 ± 17.1 mm Hg (diastolic pressure was 70.0 ± 11.5 mm Hg). The lowest arterial pressures were obtained 2 min after the injection: systolic 106.8 ± 15.6 mm Hg and diastolic 63.3 ± 9.5 mm Hg. Immediately before the administration of thiopentone mean systolic arterial pressure was 117.8 ± 17.7 mm Hg. Diastolic pressure was 71.7 ± 9.8 mm Hg. The lowest systolic and diastolic pressures, obtained 2 min after injection, were 106.7 ± 10.1 mm Hg and 69.1 ± 7.9 mm Hg respectively.

Mean (± SEM) heart rate in the midazolam group was 70.9 ± 9.6 beat min⁻¹ before induction and this increased to 77.4 ± 11.4 beat min⁻¹ 3 min after the administration of the drug.

Baseline mean (± SEM) heart rate in the thiopentone group was 69.0 ± 11.0 beat min⁻¹ which increased 3 min after injection to 75.7 ± 11.6 beat min⁻¹.

DISCUSSION

In this study the mean induction time was significantly shorter with thiopentone than with midazolam and is in agreement with similar studies by Reves and colleagues (1979) and Fragen, Gahl and Caldwell (1978). With an induction dose of midazolam 0.2 mg kg⁻¹ we obtained a mean induction time of 78 s. Reves and co-workers (1979) used the same induction dose and obtained a mean induction time of 73 s, whereas Fragen, Gahl and Caldwell (1978) using 0.15 mg kg⁻¹ obtained a value of 175 s.

When we consider the response of the patient to the dose of either drug, assessed on the basis of the standard deviation in the duration of induction, the variation between patients was smaller in the midazolam group than in the thiopentone group. This contrasts with the results obtained by Reves.

TABLE II. Induction data (mean ± SD, range in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous closing of eyes (s)</th>
<th>Disappearance of eyelash reflex (s)</th>
<th>Time to apnoea (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>57 ± 11.7 (20–65)</td>
<td>78 ± 15.3 (50–110)</td>
<td>71 ± 18.6 (40–120)</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>42 ± 10.7 (20–65)</td>
<td>61 ± 20.8 (25–130)</td>
<td>50 ± 15.3 (25–80)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TABLE III. Mean difference between thiopentone and midazolam and 95% confidence limits for difference

<table>
<thead>
<tr>
<th></th>
<th>Mean difference</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>+3.0</td>
<td>-2.0 and +8.2</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>+2.6</td>
<td>-0.8 and +6.0</td>
</tr>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>-2.0</td>
<td>-6.5 and +2.6</td>
</tr>
</tbody>
</table>
MIDAZOLAM AND THIOPENTONE

and colleagues (1979) who found a considerably greater variation in patients receiving midazolam. The reason for this might be that, besides midazolam or thiopentone, the patients in our study received fentanyl i.v. at induction and it is likely that this could potentiate the effects of midazolam.

Apnoea occurs frequently in thiopentone-induced anaesthesia (Fragen, Gahl and Caldwell, 1978). However, in the present study, no significant difference was observed in the frequency of apnoea between the two drugs (77% in the midazolam group and 83% in the thiopentone group).

No arrhythmias were observed in either group. The fact that no significant differences were found in systolic arterial pressure, diastolic arterial pressure and heart rate between the two drugs, agrees with a similar study by Fragen, Gahl and Caldwell (1978).

ACKNOWLEDGEMENT

Midazolam (Dormicum) was kindly supplied by F. Hoffmann-La Roche.

REFERENCES


ETUDE CLINIQUE SUR LES POSSIBILITÉS D'UTILISATION DU MIDAZOLAM COMME AGENT D'INDUCTION À LA PLACE DU THIOPENTAL

RESUME

Une étude prospective randomisée en simple aveugle a été entreprise pour préciser la valeur du midazolam comme agent d'induction de l'anesthésie. Soixante sujets en bonne santé subissant des actes brefs de chirurgie orthopédique ont reçu au hasard soit 0,2 mg kg⁻¹ de midazolam, soit 3 mg kg⁻¹ de thiopental. Le temps d'induction (mesuré comme délai de perte du réflexe palpitbral) était significativement plus court dans le groupe thiopental que dans le groupe midazolam. Les deux agents n'ont pas pu être distingués pour ce qui est du délai de survenue d'une apnée, des modifications de la fréquence cardiaque et de la pression artérielle.

KLINISCHE UNTERSUCHUNG ÜBER DIE ANWENDBARKEIT VON DORMICUM (MIDAZOLAM) ZUR EINLEITUNG IN VERGLEICH ZU LEOPENTAL (THIOPENTAL)

ZUSAMMENFASSUNG

In einer prospektiven, randomisierten Einfach-Blind-Untersuchung wurde über den Wert von Midazolam als Einleitungsmittel für Narkosen befunden. Sechzig Patienten gesunde, die sich einen kurzen orthopädischen Eingriff unterziehen mußten, wurden nach Randomisierung entweder für Midazolam 0,2 mg kg⁻¹ oder für Thiopental 3 mg kg⁻¹ einge- teilt. Die Einleitungszeit (gemessen als Zeit bis zum Erlöschen des Lindeflexes) war in der Thiopental-Gruppe signifikant kürzer als in der Midazolam-Gruppe. Hinsichtlich Atemstillstand, Änderungen der Pulsfrequenz und arterieller Blutdruck sind keine Unterschiede zwischen den beiden Pharmaka beobachtet worden.

USO DEL MIDAZOLAM COMO AGENTE DE INDUCCION: COMPARACION CON LA TIOPENTONA

SUMARIO

Se emprendió una investigación simple-ciega al azar de prospeción para establecer el valor del midazolam como agente de inducción de la anestesia. Sesenta pacientes sanos estaban por someterse a operaciones quirúrgicas ortopédicas de corte durante y se les administró al azar ya sea 0,2 mg kg⁻¹ de midazolam ya sea 3 mg kg⁻¹ de tiopentona. El tiempo de inducción (medido como tiempo transcurrido hasta la pérdida del reflejo de pestañear) en el grupo con tiopentona fue significativamente más corto que en el grupo con midazolam. No se observó ninguna diferencia entre las dos substancias en cuanto al tiempo de aparición de la apnea, ni tampoco hubo cambios en el ritmo cardíaco y la presión arterial.