ATROPINE REVERSAL OF HYPERCARBIA DURING ENFLURANE ANAESTHESIA

W. M. WAHBA AND J. SADKOVA

SUMMARY
Atropine was given i.v. to 35 spontaneously breathing healthy adults anaesthetized with enflurane to determine if it would reduce $P_{\text{aCO}_2}$ by improving gas exchange. Five minutes after administration of atropine, $P_{\text{aCO}_2}$ decreased from mean 7.18 to 6.65 kPa (−7%), while mean $\dot{V}E$ increased from 4.8 to 6.1 litre min$^{-1}$ (+27%). These changes were maintained 15 min later in the 20 patients studied at that time. Older and more obese patients showed a more significant change. Respiratory frequency and $P_{\text{ao2}}$ did not alter.

During a study of the pattern of breathing during enflurane anaesthesia, we found that there was a relationship between the forced expiratory volume in one second (FEV$_{1.0}$) and $P_{\text{aCO}_2}$. The increase in $P_{\text{aCO}_2}$ during anaesthesia compared with the value before anaesthesia correlated with the ratio FEV$_{1.0}$/vital capacity* while the values during anaesthesia correlated with the ratio FEV$_{1.0}$/height.f We suggested that airway resistance ($R_{\text{AW}}$) may influence the increase in $P_{\text{aCO}_2}$ occurring under general anaesthesia with spontaneous ventilation. If this is so, a reduction in $R_{\text{AW}}$ should improve pulmonary ventilation. The present study was designed to test this hypothesis by measuring expired minute volumes ($\dot{V}E$) and arterial blood-gas tensions before and after the i.v. administration of atropine in 35 healthy adult patients undergoing minor peripheral surgery. Atropine was chosen because its effects on flow resistance have been measured by Don and Robson (1965).

METHODS
Thirty-five healthy adults undergoing elective operations on the periphery of the body gave consent for the study, which was approved by the Hospital Research and Ethics Committee. Measurements were made in all patients (group I) 5 min after the injection of atropine and in 20 (group II) the measurements were repeated 20 min after injection. The 15 patients in group I who were studied only at 5 min were not distinctly different from the other patients. The biometric data are summarized in table I.

Premedication consisted of anileridine (U.S.P.) 12.5–37.5 mg and promethazine 12.5–25 mg, according to body weight, given i.m. 1 h before operation. After induction of anaesthesia with thiopentone 2–3 mg kg$^{-1}$ i.v. and orotracheal intubation facilitated by suxamethonium 1 mg kg$^{-1}$, all the subjects received enflurane in nitrous oxide 3 litre min$^{-1}$ and oxygen 2 litre min$^{-1}$ from a semi-closed circle system with carbon dioxide absorption. Ventilation was assisted manually until the patient resumed adequate spontaneous breathing. The vaporizer (Cyprane) setting of 2–3% was adjusted on the basis of arterial pressure, heart rate, lack of lacrimation and the absence of response to surgical stimulation. No change in the vaporizer setting was made during the period of study. Twenty to 30 min after the surgical incision was made, when tidal volume and frequency were steady for 5 min, $\dot{V}E$ was measured using a Wright respirometer connected to a low resistance, uni-directional valve. Tidal volume ($V_T$) was derived from the measured values of $\dot{V}E$ and breathing frequency ($f$). The measured values were not corrected to BTPS. Arterial blood was obtained from a radial artery anaerobically into heparinized syringes, which were packed in ice. Blood-gas tensions and pH were determined within 10 min using standard electrodes calibrated with 0.5 and 10% carbon dioxide (Corning 165 blood-gas analyser). The results were not corrected for time, introducing a
possible error of 0.07–0.01 kPa for $P_{aCO_2}$ (Kelman and Nunn, 1966).

Atropine 0.01 mg kg$^{-1}$ was injected i.v. and the measurements repeated 5 min later in all patients, and 20 min after the injection in 20 patients.

Statistical analysis of the data was performed using Student's $t$ test, two-way analysis of variance and by regression analysis using the least squares method.

RESULTS

There were no significant differences between the two groups with respect to age and body build (table I) or in the blood-gas and ventilation values before the administration of atropine (table II). Ventilation before atropine in the 15 patients studied at 5 min was slightly greater than that in the other 20 patients ($P<0.1$) but there was no significant difference in $P_{aCO_2}$.

Five minutes after the injection of atropine, mean $\dot{V}_E$ increased by 27% from 4.8 ± 0.18 to 6.1 ± 0.24 litre min$^{-1}$ in group I ($P<0.001$). In group II, mean $\dot{V}_E$ also increased by 27% from 4.49 ± 0.21 to 5.69 ± 0.28 litre min$^{-1}$ ($P<0.001$). Arterial $P_{aCO_2}$ in group I decreased by 7% from 7.18 ± 0.16 to 6.65 ± 0.19 kPa ($P<0.001$). In group II, mean $P_{aCO_2}$ before atropine was 6.91 ± 0.17 kPa and mean $P_{aCO_2}$ 5 min after atropine was 6.17 ± 0.20 ($P<0.001$).

The measurements at 5 min in group II were maintained at 20 min (table II) without any significant difference between the values at these time intervals. For analysis of these data, two-way analysis of variance and Student's $t$ test were used.

Respiratory frequency, $P_{aO_2}$, pH and standard bicarbonate did not change significantly at any time in either group.

The values of $\dot{V}_E$ were standardized to allow for differences in size between individuals by the use of

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group I (n = 35)</th>
<th>Group II (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{aO_2}$ (kPa)</td>
<td>Before</td>
<td>19.16 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>19.06 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>n.s.</td>
</tr>
<tr>
<td>$HCO_3^-$ (mmol litre$^{-1}$)</td>
<td>Before</td>
<td>22.6 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>20.7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>n.s.</td>
</tr>
<tr>
<td>pH (unit)</td>
<td>Before</td>
<td>7.25 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>7.26 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>n.s.</td>
</tr>
<tr>
<td>$P_{aCO_2}$ (kPa)</td>
<td>Before</td>
<td>7.18 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>6.65 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$f$ (b.p.m.)</td>
<td>Before</td>
<td>16.0 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>16.0 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>n.s.</td>
</tr>
<tr>
<td>$VT$ (ml)</td>
<td>Before</td>
<td>316.9 ± 15.2</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>374.2 ± 17.4</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\dot{V}_E$ (litre min$^{-1}$)</td>
<td>Before</td>
<td>4.8 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>6.1 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\dot{V}_E/SA$ (litre min$^{-1}$ m$^{-2}$)</td>
<td>Before</td>
<td>2.66 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>5 min after</td>
<td>3.39 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
the ratio $\dot{V}_E$/surface area (SA). Mean $\dot{V}_E$/SA for all subjects increased from $2.66 \pm 0.1$ to $3.39 \pm 0.13$ litre min$^{-1}$ m$^{-2}$ 5 min after atropine ($P<0.001$). In group II patients, $\dot{V}_E$/SA increased from $2.46 \pm 0.10$ to $3.13 \pm 0.15$ litre min$^{-1}$ m$^{-2}$ ($P<0.001$); at 5 min, a value not significantly different from that noted at 20 min ($3.21 \pm 0.16$ litre min$^{-1}$ m$^{-2}$). Figure 1 shows the observed mean values of $P_{aCO_2}$ and $\dot{V}_E$/SA in the two groups at the stated time intervals.

![Graph](image1)

**Fig. 1.** Changes in mean $P_{aCO_2}$ and $\dot{V}_E$/SA before and after administration of atropine.

The relationship between $\dot{V}_E$/SA and $P_{aCO_2}$ for all the data is shown in figure 2. This relationship is expressed by the following equation:

$$P_{aCO_2} = 8.5 - 0.61 \dot{V}_E$/SA \quad (r = 0.51, P<0.001)$

**DISCUSSION**

The anaesthetic technique used in this study may be criticized because alveolar concentrations of the anaesthetic agents were not identical. However, we believe that it is preferable to use the standard technique appropriate for the surgery.

The purpose of the present study was to determine if the i.v. injection of atropine during enflurane anaesthesia would have beneficial effects on gas exchange. Although there were individual differences in the degree of change in $P_{aCO_2}$ in our patients, mean $P_{aCO_2}$ decreased and mean ventilation increased markedly following the injection of atropine. These changes may result from a reduction in airway resistance or central stimulation of ventilation.

Central stimulation would cause an increase in respiratory rate or tidal volume, or both. We found no change in respiratory frequency, but the effect may have been masked by narcotic premedication. An increase in central respiratory drive can be measured by comparing the tracheal pressures generated during airway occlusion ($P_O$) at functional residual capacity (FRC) before and after atropine. These measurements would differentiate between changes in central inspiratory drive and peripheral effects (Milic-Emili and Grunstein, 1976). We performed these measurements in four other subjects (G. B. Drummond and W. M. Wahba, unpublished observations) premedicated with diazepam and anaesthetized with enflurane in a mixture of nitrous oxide in oxygen and found no changes in occlusion pressure or in the ratio of inspiration to expiration. Frequency was unchanged also.

These preliminary results suggest that the main site of action of i.v. atropine is peripheral rather than central. Mean flow rates must have increased following the injection of atropine, probably as a result of reduced airway resistance. There are conflicting reports on the effects of atropine on $R_{AW}$ during
anaesthesia. Don and Robson (1965) reported that
total flow resistance in patients anaesthetized with
nitrous oxide was decreased by 33% following
atropine in the same dosage as was used in our study.
On the other hand, Brakensiek and Bergman (1970)
reported that atropine 0.8 mg i.v. during halothane
anaesthesia reduced $R_{AW}$ only in subjects with
pre-existing high airways resistance. In awake
subjects, $R_{AW}$ is reduced markedly by atropine
(Vincent et al., 1970). These authors found that total
pulmonary resistance during both inflation and
deflation was reduced, with a greater effect during
inflation. They confirmed also that lung volume
history influences resistance. Daly, Ross and Behnke
(1963) reported a small reduction in $R_{AW}$ following
atropine in awake man. Groto, Whitman and Arakawa
(1978) have reported recently that i.v. atropine
0.008 mg kg$^{-1}$ significantly increased expiratory flow
functions (FEV$_{1.0}$%, maximum mid-expiratory flow
and maximum expiratory flow at 50% total lung
capacity) with a small, transient and insignificant
decrease in $R_{AW}$. The authors interpreted these
observations in six awake volunteers as a decrease in
small airways resistance. The improvement in
expiratory flow functions was detectable 10 min
after injection and lasted longer than 1 h. Thus the
bulk of evidence supports the thesis that our results
may be explained on the basis of a reduction in $R_{AW}$.

The lack of a relationship between $\dot{V}E/SA$ and
$P_{ACO_2}$ with time of measurement (fig. 2) is a reflection of
individual variability in the change in $P_{ACO_2}$ and in
deadspace, and of the non-steady state. Analysis of
individual data at 5 min revealed that the extent of
change in $P_{ACO_2}$ could be related to the age and body
build of the patient. By arbitrarily choosing a change in
$P_{ACO_2}$ greater or less than 0.67 kPa, we subdivided
our subjects into two groups (table III). The patients
with greater reductions in $P_{ACO_2}$ (mean change of
$-0.97$ kPa) were older and more obese ($P<0.05$).
These patients showed a greater increase in $\dot{V}E/SA$
($P<0.01$) and a greater decrease in $P_{ACO_2}$ ($P<0.001$)
after atropine. It is known that the reduction in FRC
following the induction of anaesthesia is greater in
older subjects (Hewlett et al., 1974) and also in
patients with high weight : height ratios (Don et al.,
1970). An inverse relationship exists between lung
volume and airway resistance. Greater improvements
following atropine may be expected in patients with
smaller FRC values where airways resistance has a
more marked influence on ventilation. However,
obese patients received a larger dose of atropine, since
dosage was based on body weight. If this increase in
dose was inappropriate, the changes may be a reflec-
tion of a dose-response relationship.

Changes in $\dot{V}E$ precede those in $P_{ACO_2}$ because of
the size of the body stores of carbon dioxide. Con-
sequently, the disproportionate increase in $\dot{V}E$
(+27%) compared with the decrease in $P_{ACO_2}$ (−7%)
may indicate that a steady state was not present 5 min
after injection of atropine. Fifteen minutes later a
more clearly defined difference in the distribution of
the data relative to the time of measurement could be
noted (fig. 3). However, the reduction in $P_{ACO_2}$ may
have been limited by the increasing deadspace and
the deepening of anaesthesia. By inference, a steady
state was probably absent at 20 min.

<table>
<thead>
<tr>
<th>TABLE III. Data grouped for patients who exhibited a change in $P_{ACO_2}$ greater or less than 0.67 kPa following i.v. atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Before</td>
</tr>
<tr>
<td>Change &lt; 0.67 kPa</td>
</tr>
<tr>
<td>3.4</td>
</tr>
<tr>
<td>Change &gt; 0.67 kPa</td>
</tr>
<tr>
<td>5.1</td>
</tr>
<tr>
<td>$P$</td>
</tr>
</tbody>
</table>
ATROPINE AND $P_{\text{CO}_2}$ DURING ENFLURANE ANAESTHESIA

Fig. 3. Relationship between $\dot{V}E/SA$ and $P_{\text{CO}_2}$, before and 20 min after atropine (group II). There is a distinct trend with reference to time of sampling. $\bigcirc =$ before; $\bigbullet =$ 20 min after.

Hypercarbia causes bronchodilatation (Aviado, 1975) and it is surprising that atropine can still exert such an effect under these circumstances.

The clinical implications of this study are that hypercarbia during enflurane anaesthesia can be limited but not reversed by the use of atropine, particularly in older and more obese patients.

ACKNOWLEDGEMENTS

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REFERENCES


RESUME

On a administre de l’atropine par voie intraveineuse a 35 adultes en bonne sante, respirant spontanement, anesthesies a l’aide d’enflurane, pour voir si l’on pourrait reduire la $P_{\text{CO}_2}$, en ameliorant l’echange de gaz. Cinq minutes apres l’administration d’atropine, la $P_{\text{CO}_2}$ a diminue d’une moyenne de 7,18 a 6,65 kPa (—7%), alors que le $\dot{V}E$ moyen a augmenté de 4,8 a 6,1 litre min$^{-1}$ (+27%). Ces variations existaient toujours 15 min plus tard sur les 20 patients qui faisaient a ce moment-la l’objet de l’etude. Les patients plus ages et plus obeses ont accusé des variations plus prononcees. La frequence respiratoire et la $P_{\text{O}_2}$ n’ont pas ete modifiees.

ZUSAMMENFASSUNG

Atropin wurde intravenös an 35 spontan atmende, gesunde Erwachsene verabreicht, die mit Enfluran narkotisiert waren; es sollte festgestellt werden, ob dies durch verbesserten Gas Austausch zu einer Verringerung von $P_{\text{CO}_2}$ führte. Fünf Minuten nach Verabreichung der Droge sank $P_{\text{CO}_2}$ von einem Mittelwert von 7,18 auf 6,65 kPa (—7%), während der Mittelwert von $\dot{V}E$ von 4,8 auf 6,1 Liter min$^{-1}$ (+27%) anstieg. Diese Veränderungen blieben erhalten bei den 20 Patienten, die 15 Min später untersucht wurden. Ältere und fettleibigere Patienten zeigten stärkere Veränderungen. Respirationsrate und $P_{\text{O}_2}$ veränderten sich nicht.
INVERSION POR ATROPINA DE HIPERCAPNIA DURANTE ANESTESIA DE ENFLURANO

SUMARIO
Se administró atropina intravenosamente a 35 adultos saludables anestesiados con enflurano que respiraban espontáneamente, a fin de determinar si se reduciría el $P_{aCO_2}$ mediante el mejoramiento del intercambio de gas. Cinco minutos después de la administración de atropina, el $P_{aCO_2}$ disminuyó de un promedio de 7,18 a 6,65 kPa (−7%), mientras que el $Ve$ aumentó de 4,8 a 6,1 litros min⁻¹ (+27%). Estos cambios continuaban 15 min más tarde en los 20 pacientes estudiados en esa oportunidad. Los pacientes de más edad y más obesos acusaron un cambio más significativo. La frecuencia del $PaO_2$ no variaron.