THE RESPIRATORY RESPONSE TO CARBON DIOXIDE DURING INNOVAR-NITROUS OXIDE ANAESTHESIA IN MAN

BY

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SUMMARY

In seven patients anaesthesia was induced by injection of a single dose of Innovar and maintained with nitrous oxide and oxygen. Marked respiratory depression persisted for longer than one hour. Tidal volume, respiratory rate and minute volume measurements were inadequate indicators of this effect which is well shown by measurement of end-tidal carbon dioxide tension. The best quantitation is the slope of the ventilatory response to elevated carbon dioxide tension, determined in l./min/mm Hg. Displacement of the response curve was very variable after loss of consciousness. The data indicate that spontaneous respiration with this anaesthetic technique, as with the majority of other general anaesthetics, is accompanied by respiratory acidosis.

Neuroleptanaesthesia is currently provided by various combinations of butyrophenones and narcotic analgesics together with nitrous oxide. Adequate respiration during the neuroleptic state has been reported by some (deCastro, 1964; Foldes, 1964), while others have found an undesirable degree of respiratory acidosis (Dobkin et al., 1963; Corsen, Domino and Sweet, 1964). Since the respiratory response to carbon dioxide stimulation provides the most sensitive index of respiratory depression (Lambertsen, 1966), we have used this technique to measure the degree and time course of the respiratory effects of Innovar and nitrous oxide anaesthesia in man. A discussion of the problems involved in the measurement of the respiratory effects of drugs is also included.

METHODS

Seven patients, free of cardiopulmonary disease, agreed to an extra period of anaesthesia with neuroleptic drugs after the purpose and techniques of the study were explained to them. Each received premedication consisting of Innovar 1 ml/100 lb. Thirty to forty minutes later, the ventilatory response was measured over a range of end-tidal carbon dioxide of approximately 15 mm Hg.

Since it is difficult to obtain a steady state during carbon dioxide challenge in unpremedicated patients anticipating anaesthesia and operation, we elected to study patients after premedication and to compare results with predicted values. Patients were studied prior to operation in a quiet, dark room to decrease external stimuli. The end-tidal carbon dioxide tension was taken from a tidal volume more than three times the size of the predicted anatomical deadspace, with one exception. End-tidal carbon dioxide tension was measured rather than arterial to avoid the stimulation of an arterial puncture.

† Resting end-tidal carbon dioxide values significantly different from arterial because of inadequate depth of respiration and an inadequate deadspace washout would give a curvilinear carbon dioxide response in the lower segment. This was not found. We estimate the maximal difference between end-tidal and arterial that might exist, due to this effect, would be 1.5 mm Hg. An increase of this magnitude would not change the interpretation of the data. An increased A-a difference for carbon dioxide might also arise from atelectasis during the unchallenged interval as the result of slow monotonous ventilation following the narcotic. Such an effect would be overcome in part by the deep breathing with carbon dioxide challenge resulting in a systematically higher end-tidal carbon dioxide in the resting period after the challenge compared to the resting period before challenge. No such difference was seen.

* Innovar was supplied by McNeil Laboratories, Fort Washington, Pennsylvania. It consists of fentanyl, 0.05 mg/ml, and dehydrobenzperidol, 2.5 mg/ml.
Anaesthesia was induced over a 5-minute period with an intravenous drip of 5 ml Innovar in 100 ml of 5 per cent glucose in water. Only one patient required an additional dose of fentanyl, 0.05 mg, 35 minutes after induction. Three to four minutes after the infusion was begun nitrous oxide-oxygen was administered by mask with flows of 2 l./min of oxygen and 4 l./min of nitrous oxide. Spontaneous respiration was permitted as long as the patient would respond to a command to breathe. With loss of consciousness and apnoea, suxamethonium was given intravenously and the trachea intubated. Spontaneous respiration reappeared within 10 minutes. Respiration was assisted briefly until spontaneous efforts could maintain a \( P_{\text{CO}_2} \) below 65 mm Hg. Unassisted spontaneous respiration continued through the next hour of anaesthesia.

The carbon dioxide challenge was repeated 10 minutes after induction in four patients, and 30 and 60 minutes after induction in all seven. Ventilation produced by end-tidal carbon dioxide tensions approximately 6 and 12 mm Hg above the unstimulated end-tidal carbon dioxide tension was recorded. A straight line fitted by eye to the four points was plotted; the two points of elevated carbon dioxide tension and ventilation, and the carbon dioxide tensions and ventilation immediately before and after the challenges.

The patients breathed through a standard circle absorption anaesthesia system with an Air-Shields Ventimeter. A large-bore three-way valve permitted substitution of a spirometer for the breathing bag when added. Ventilatory records were made during low inflow anaesthesia in five cases. In the other two instances the recorded ventilation was corrected for the inflow of fresh gas by timing the duration of inspiration and expiration on a rapidly revolving drum on the spirometer. Carbon dioxide was added through a flowmeter to the inspiratory gas. End-tidal carbon dioxide was measured by a Liston-Becker LB-1, sampling at the rate of 500 ml/min from a needle axially placed midway down the endotracheal tube. The gas sampled was returned to the anaesthetic system. The analyzer was calibrated with mixtures of carbon dioxide and oxygen previously analyzed by the micro-Scholander technique. Spectral overlap of nitrous oxide was avoided by filling the head of the analyzer with nitrous oxide under pressure. Further correction was made for the collision-broadening effect of nitrous oxide (Severinghaus, 1960). All gas volumes refer to body temperature and pressure saturated with water vapour. Statistical assessment was by the technique of analysis of variance (Linquist, 1956), using the 5 per cent level of significance for the F ratio.

**RESULTS**

The results are summarized in tables I and II. Although the tidal volume appeared to be depressed 20 per cent after premedication, this was not significantly different from the predicted normal. After induction of anaesthesia the tidal volume was larger than after premedication on the average, but again was not significantly different from either the premedication value or the predicted normal value. Measurement of respiratory frequency was no better an index of respiratory depression. The frequency slowed down with induction of anaesthesia in every subject. Thirty minutes later it was still slow. However, by one hour after induction it had risen to within the normal range. The respiratory minute volume was a somewhat better index of respiratory depression. Premedication significantly reduced the minute volume and induction of anaesthesia resulted in a further significant decrease. Sixty minutes after induction the minute volume was larger than the previous measurements, representing a significant increase although still well below the predicted normal. In summary, these three common measures of respiration suggested that after one hour the respiratory depression occurring during Innovar anaesthesia had improved markedly.

Quite a different view was obtained from the inspection of the end-tidal carbon dioxide data. No apparent depression was seen after premedication. A marked respiratory acidosis existed 30 minutes after induction of anaesthesia, and this was unchanged at 60 minutes.

Since respiratory depression both decreases ventilation and increases carbon dioxide tension, the full effect of a depressant cannot be described by either parameter alone. The carbon dioxide challenge test evaluates both. To describe fully the line representing respiratory response to increasing carbon dioxide one must quote a slope and an intercept on either the ventilation or carbon dioxide axis. Depressants affect both but to
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TABLE I
Ventilation after Innovar-nitrous oxide. Mean values and standard errors from seven healthy subjects.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Predicted normal</th>
<th>After premedication</th>
<th>After induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT (l.)</td>
<td>0.373</td>
<td>0.296</td>
<td>0.372</td>
</tr>
<tr>
<td>SE</td>
<td>0.060</td>
<td>0.140</td>
<td>0.080</td>
</tr>
<tr>
<td>% of normal</td>
<td>100</td>
<td>79.3</td>
<td>99.8</td>
</tr>
<tr>
<td>f (b.p.m.)</td>
<td>16</td>
<td>15.0</td>
<td>14.0</td>
</tr>
<tr>
<td>SE</td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>% of normal</td>
<td>100</td>
<td>93.7</td>
<td>72.5</td>
</tr>
<tr>
<td>VE (l./min)</td>
<td>5.973</td>
<td>4.129</td>
<td>3.386</td>
</tr>
<tr>
<td>SE</td>
<td>0.478</td>
<td>0.546</td>
<td>1.022</td>
</tr>
<tr>
<td>% of normal</td>
<td>100</td>
<td>69.1</td>
<td>56.7</td>
</tr>
<tr>
<td>PETCO₂ (mm Hg)</td>
<td>40</td>
<td>39.5</td>
<td>45.0</td>
</tr>
<tr>
<td>SE</td>
<td>1.9</td>
<td>1.6</td>
<td>3.4</td>
</tr>
<tr>
<td>% of normal</td>
<td>100</td>
<td>98.8</td>
<td>88.8</td>
</tr>
</tbody>
</table>

VT is tidal volume in litres BTPS. Respiratory frequency is f. Minute volume, VE, is in litres BTPS. PETCO₂ is end-tidal carbon dioxide tension. The tidal values are not significantly different. Of the frequency, only the value 30 minutes after induction is significantly reduced. All four values of minute volume are significantly different from each other. End-tidal carbon dioxide is not significantly altered by premedication but is significantly increased both 30 and 60 minutes after induction.

TABLE II
Ventilatory response to carbon dioxide after Innovar-nitrous oxide. Mean values and standard errors from seven healthy subjects.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Predicted normal</th>
<th>After premedication</th>
<th>After induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pco₁₀¹ (mm Hg)</td>
<td>42.7</td>
<td>46.9</td>
<td>55.4</td>
</tr>
<tr>
<td>SE</td>
<td>1.8</td>
<td>7.8</td>
<td>4.0</td>
</tr>
<tr>
<td>% of normal</td>
<td>100</td>
<td>109.8</td>
<td>129.7</td>
</tr>
<tr>
<td>ΔPco₁₀¹</td>
<td>0</td>
<td>4.2</td>
<td>12.7</td>
</tr>
<tr>
<td>SE</td>
<td>1.8</td>
<td>7.8</td>
<td>4.0</td>
</tr>
<tr>
<td>ΔVE/ΔPco₁₀¹ (l./min Hg/min)</td>
<td>1.5</td>
<td>1.04</td>
<td>0.64</td>
</tr>
<tr>
<td>SE</td>
<td>0.11</td>
<td>0.09</td>
<td>0.15</td>
</tr>
<tr>
<td>% of normal</td>
<td>100</td>
<td>69.3</td>
<td>42.7</td>
</tr>
</tbody>
</table>

Pco₁₀¹ is the end-tidal carbon dioxide necessary to produce a ventilation of 10 l./min, BTPS. ΔVE/ΔPco₁₀¹ is the slope of the ventilatory response curve. All of the values after premedication and all after induction are significantly different from normal. The apparent return toward normal in Pco₁₀¹ and ΔPco₁₀¹ is not significant, due to considerable individual variation, but the small improvement with time in the slope of the response curve is significant.

Innovar-nitrous oxide anaesthesia the slope of the respiratory response to carbon dioxide challenge shows a severe degree of depression with only moderate restitution towards normal by 60 minutes (table II; fig. 1). At 30 and 60 minutes different extents in different situations. The normal slope in our laboratory is 1.5 l./min/mm Hg (Smith et al., 1967).
The time course of depression measured by the slope of the carbon dioxide response curve following premedication with Innovar and induction of Innovar-nitrous oxide anaesthesia in seven patients. The slope, in l./min/mm Hg, is taken from a line fitted by eye to four steady state points. The degree of depression is expressed as the percentage of the predicted awake response. Depression to two-thirds of the awake response was present 30 minutes after premedication. Ten minutes after induction the respiration of three patients was still controlled so that the 11 per cent value refers to only four of the seven subjects. One hour after induction the response was only one-half of normal, but was improving, as all seven had lower responses at 30 minutes.

post-induction the rate of response was 0.64 and 0.74 l./min/mm Hg, respectively. The improvement was seen in all seven patients.

The intercept data in table II are for 10 l./min. In studies of narcotics, the Pco₂ leading to a 20 l./min ventilation is usually selected. Most of the patients in this study did not achieve this ventilation despite an increase in end-tidal carbon dioxide of 12–15 mm Hg above the resting tension. Therefore, we chose a ventilation of 10 l./min at which to express the Pco₂. The predicted normal end-tidal carbon dioxide producing this ventilation is 43 mm Hg. On the average this parameter showed respiratory depression following premedication, marked depression following induction of anaesthesia, and a tendency toward improvement after 60 minutes. There was considerable scatter in the data, however, as shown by the large standard error of the mean. Because of the large variation among individuals, as illustrated in fig. 2, the analysis of variance failed to show a significant difference between the 60-minute point and the premedication point. Such differences were clearly indicated in the slope parameter. No changes of clinical significance were seen in the patients' blood pressure, pulse rate, or temperature.

It is clear from these data that Innovar-nitrous oxide exerts a consistent depressant effect on the slope of the carbon dioxide response curve. This change is dose-related as shown in fig. 3, as well
as time-related as shown in fig. 1. Figure 3 illustrates the wide range of displacement of the carbon dioxide response curves among individuals. This displacement is not correlated with either dose or time of injection.

DISCUSSION

Over the years the respiratory effects of a drug have been quantitated simply by measuring respiratory rate, tidal volume, minute volume, end-expired carbon dioxide, or, in greater detail, by adding carbon dioxide and noting the increase in minute volume at different levels of end-expired or arterial carbon dioxide. Our studies, as those of others, indicate that the carbon dioxide challenge affords the most sensitive index of drug effect. They also clearly indicate that both the displacement of the curve as well as any change in its slope must be considered.

In awake man after administration of clinical doses of fentanyl, as well as other narcotic analgesics, there is a consistent displacement of the carbon dioxide response curve to the right with little change to the slope (Smith et al., 1967). With loss of consciousness after narcotics a different effect is seen. There is a consistent decrease in the slope of the response (Forrest and Bellville, 1964), but an unpredictable inconsistent effect on displacement. The same observation has been made during inhalation anaesthetics (Munson et al., 1966). There is thus a qualitative difference between responses elicited before and after loss of consciousness. We conclude that at least two distinct mechanisms are involved in the production of respiratory depression by drugs.

During general anaesthesia a number of factors affect the control of respiration including external stimulation, the level of narcosis and the level of intracerebral carbon dioxide tension. Neither change in slope of the carbon dioxide response curve nor its displacement alone permits description of the balance of factors responsible for the ventilation existing under a particular set of circumstances. But the change in slope does permit quantification of the effects of Innovar-nitrous oxide so far as dosage and time are concerned. It is evident that this form of neuroleptanalgesia depresses respiration profoundly, its maximal effect resembling the respiratory effect of 2.5 times the minimum anaesthetic concentration (MAC) of fluoroxene or 2–2.5 MAC halothane (Munson et al., 1966).

ACKNOWLEDGEMENTS

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REFERENCES


LA REPONSE RESPIRATOIRE AU BIOXYDE DE CARBONE PENDANT L'ANESTHESIE A L'INNOVAR-PROTOXYDE D'AZOTE CHEZ L'HOMME

SOMMAIRE

Chez 7 patients l'anesthésie a été induite par l'injection d'une dose unique d'Innovar et maintenue par un mélange de protoxyde d'azote et d'oxygène. Une dépression respiratoire marquée persiste pendant plus d'une heure. La mesure de la fréquence respiratoire et des volumes circulants ainsi que le volume minute étaient des critères inutiles pour cet effet qui est bien mis en évidence par la mesure de la tension du bioxyde de carbone terminal. La meilleure estimation est obtenue des variations de la réponse ventilatoire à une tension élevée de bioxyde de carbone exprimée en
BOOK REVIEW


In his preface, Dr. Caro explains that this book is neither a comprehensive textbook nor an exhaustive review of recent literature. It is intended as a series of reviews of eight circumscribed aspects of respiratory physiology, with particular emphasis placed upon the growing points. Dr. Caro is to be congratulated on a masterly choice of both subjects and authors. All eight subjects are of great interest and in most cases have seen advances which are so recent that they have not yet received adequate treatment in general textbooks on respiration.

The first chapter, dealing with "Cerebrospinal fluid and the regulation of respiration", is contributed by Dr. R. A. Mitchell who has been involved in most of the recent studies which have revolutionized our understanding of the mechanism by which carbon dioxide is concerned in the regulation of respiration. The relevance of this work to anaesthesia is evident and it is appropriate that Dr. Mitchell is himself a member of the Department of Anesthesiology at the University of California, San Francisco. The second chapter (by Dr. J. G. Widdicombe) covers the neglected subject of the "Regulation of bronchial calibre" and studies by a number of anaesthetists feature in the chapter.

"Surface tension and the lining of the lung alveoli" is now a familiar topic and, in chapter 3, the subject is reviewed by Dr. R. E. Pattle who started the present wave of interest in the field by publishing the reports of his now classical studies in 1955. He is cautious in ascribing clinical conditions to absence of the surfactant but his terminal note of "Unsolved problems" reveals the degree of the present state of ignorance of the subject. Chapter 4 (Dr. F. P. Chinard) is devoted to the "Permeability characteristics of the pulmonary blood-gas barrier" and is strikingly different from the well-worn textbook passages on diffusibility of oxygen and carbon dioxide through the alveolar-capillary membrane. Particularly welcome is the unaccustomed attention paid to the permeability of the barrier to water, electrolytes, anaesthetic gases and a range of other substances. Attention is also paid to the feasibility of flushing noxious substances from the respiratory system by the intra-tracheal instillation of various aqueous solutions. Many of the references will be unfamiliar to anaesthetists and will be valuable.

In chapter 5, Dr. L. E. Farhi is on more familiar ground in a review of "Ventilation-perfusion relationship and its role in alveolar gas exchange". This is a straight but lucid presentation of a difficult subject, in which Dr. Farhi is an expert both in investigation and in exposition. In similar vein, Dr. J. B. West (chapter 6) reviews "Regional differences in blood flow and ventilation in the lung", a subject in which his own contribution is so outstanding.

Dr. C. G. Caro, in chapter 7, takes the reader through the difficult subject of the "Mechanics of the pulmonary circulation". Despair will have greeted many who have tried to read up this notorious subject and this chapter will be welcomed, particularly in view of the scant treatment which it has received in a number of recent books. The final chapter is on "Tissue respiration" by Dr. I. S. Longmuir and fills a grievous and longstanding gap in the field of respiratory physiology. Most students of the subject are familiar with the factors influencing the conveyance of oxygen to the cell, but are content to draw a veil over what happens next. Apart from a vague realization of the existence of histotoxic anoxia, the field is usually abandoned to the biochemist. Dr. Longmuir gives a most readable account of "What happens to the oxygen" and lends purpose to the traditional accounts of oxygen transport.

After the recent publication of so many excellent books on respiration, it might be thought that there was little else to be said. Dr. Caro and his authors have shown us how mistaken we are in this view. They have selected eight important and often misunderstood subjects and dealt with them in depth with important implications in the field of anaesthesia, that it must also be recommended for all who are interested in the respiratory implications of anaesthesia.

J. F. Nunn