A Controlled Study of Three Respiratory Stimulants in Chronic Respiratory Failure

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The effects of slow intravenous infusion of three different respiratory stimulants (dimeffine, nikethamide and prethcamide) on minute and alveolar ventilation, blood gases and pH were studied in 18 patients with chronic pulmonary emphysema and chronic respiratory failure. For a more accurate assessment of the results of the double blind controlled trial, a factorial design in a Youden square scheme was employed. Respiratory rate, tidal volume, minute ventilation, arterial Po2, pH and heart rate failed to show significant changes after the intravenous infusion of the drugs. The other parameters studied (dead space, alveolar ventilation, CO2 output, Paco2) showed some differences but these were temporally similar for the three drugs. As improvement in respiratory and blood gases data was transient and slight and undesirable side-effects constant, it is concluded that the use of respiratory stimulants in management of chronic respiratory failure cannot be recommended.

INTRODUCTION

In the hope that ventilatory stimulation could lead to improved carbon dioxide elimination and arterial oxygenation in respiratory failure, many new agents have been given clinical trials in recent years.1-4 In respiratory failure, therapeutic efficacy can be judged by reduction in blood Paco2 and by ability to administer oxygen without precipitation of respiratory acidosis. While some investigators report increased arterial Po2 and pH and decreased Paco2 after administration of different respiratory stimulants,1-3,8-10 the very narrow margin between therapeutic and toxic effect and short duration of action of these drugs have precluded general clinical acceptance.11,12 In general, these studies have suffered from poor experimental design and statistical evaluation. In addition, the varied clinical material and methods employed have resulted in some disagreement in published reports.

In a prior investigation, the effects of three respiratory stimulants on external ventilation were reported.13 These drugs, nikethamide, dimeffine, and prethcamide, had similar effects on some respiratory parameters. Minute ventilation was increased chiefly as a consequence of an increased respiratory rate. In this investigation, the same three drugs were studied to assess effects on alveolar ventilation, blood gases, and pH in chronic obstructive respiratory failure.

MATERIAL AND METHODS

Eighteen hospitalized patients were studied during a period of relative clinical stability. There were 15 men and three women, and each had chronic pulmonary emphysema and chronic respiratory failure. American Thoracic Society Committee diagnostic criteria were employed. Respiratory function tests were used to assess the extent of clinical derangement and to exclude a relevant degree of bronchospasm. Table 1 summarizes clinical data, ventilatory capacity, arterial blood gas tensions, and pH. With the exception

| Table 1—Functional and Blood Gas Data, (Values Are Mean ± S.D.) |
|-------------------|---------|
| No. of cases | 18      |
| Age             | 62.27 ± 5.05 |
| VC/VC predicted × 100, % | 52.88 ± 14.27 |
| MVV/MVV predicted × 100, % | 26.15 ± 8.96 |
| RV/TLC × 100, % | 60.30 ± 10.24 |
| FEV1/VC × 100, % | 46.40 ± 10.85 |
| PaCO2, mm Hg | 52.11 ± 8.49 |
| PaO2, mm Hg | 49.17 ± 9.84 |
| pH              | 7.385 ± 0.066 |
of ampicillin, no therapy was given during the course of study. Intelligent cooperation on the part of the patient was insured by basal conditions and by careful adaptation to equipment and techniques used. The tests were performed at the same time of the day and by the same investigators for each patient.

Effects on minute and alveolar ventilation, on carbon dioxide elimination and arterial gas tensions, and on pH were studied after intravenous infusion of the drugs. Drugs tested were dimenline (40 mg), nikethamide (1.875 mg), and prethcamide (1.125 mg). These were supplied to the investigators in identical ampules labelled A, B and C and used in double-blind fashion according to a previously randomized scheme.

The patient was in a semirecumbent position and was connected by a well-fitting mouthpiece to an open circuit apparatus. A slow intravenous drip of isotonic saline solution was given. Under local 1 per cent procaine anesthetic, a thin-walled Riley needle was inserted into the brachial artery. After resting for 10 to 20 minutes in this position, the patient's expired air was collected in a 150 liter Douglas bag for five minutes (Time 0), respiratory rate was noted, and arterial blood was collected at the midperiod of air collection in a 10 ml Luer-Lok oiled syringe with heparin used to fill the dead space. It was thus possible to estimate respiratory rate, tidal volume, minute ventilation, CO₂ output, arterial Po₂, Pco₂, and pH. Dead space and alveolar ventilation were calculated from Bohr's equation solved for Paco₂.

The drug was then infused over 20 minutes. The patient was not aware of the change in infusion. The same parameters were recorded at minutes 6 to 10 (Time 1), 16 to 20 (Time 2), and 40 to 44 (Time 3) from the beginning of drug administration.

According to the experimental design, only two drugs (each in a different day) were studied in each patient.

Expired air was measured with a dry gas meter connected to the Douglas bag. Paco₂ was measured with a modified Clark's Teflon-covered Pt electrode (Eschweiler, Kiel, Germany). A Severinghaus CO₂ electrode (Eschweiler) and a Radiometer glass electrode were used for measurement of Paco₂ and pH. Known gas concentration, analyzed in a Scholander apparatus, and tonometered blood were used for calibration. All measurements were made in duplicate within three minutes from sampling. Duplicate analyses were required to check within ± 1 mm Hg for arterial Po₂ and Paco₂ and within ± 0.001 for pH. Carbon dioxide concentration in expired air was measured with the Scholander microanalyzer. All analyses were performed in duplicate and required to check within 0.02 volumes. All determinations were made in Perugia (altitude 500 m above sea level, barometric pressure 730 to 740 mm Hg), and all respiratory volumes and ventilation data were corrected at BTPS; carbon dioxide output was corrected at STPD. In each case, heart rate and blood pressure were recorded before, during, and after the tests. Side-effects were carefully noted.

**Statistical Analysis**

The 18 patients were divided into three groups of six. As the complexity of the procedure made it difficult to test three drugs in each patient, an experimental design with incomplete balanced blocks was used and only two drugs were studied in each case. Each patient thus repeated the test twice with two different drugs according to a previously randomized scheme, and each drug was therefore studied 12 times. The Youden square design was employed as it provided the same advantages of a Latin square scheme (Fig 1). Both the differences between patients and between days of testing were thus controlled. The factorial design seemed to be the most appropriate for this study. Drugs and times were the two main factors in this trial and each was studied at different levels, ie, 3 for the drugs and 4 for the times (minutes 0, 6 to 10, 16 to 20, and 40 to 44) (3 × 4).

**Results**

The mean values of the various parameters studied, adjusted for Youden square, are summarized in Table 2. The data are given for prethcamide, nikethamide, and dimenline at times 0, 1 (6 to 10 minutes), 2 (16 to 20 minutes), and 3 (40 to 44 minutes). The following parameters failed to show significant change after the intravenous infusion of the drugs: respiratory rate, tidal volume, minute ventilation, Paco₂, pH, and heart rate (Table 3, Fig 2). The other parameters studied did show some differences but these were temporally similar for the three drugs. This is demonstrated by the lack of a significant interaction between drugs and times. The following summarizes these results (mean values) for the three drugs independent of time and for the four times independent of the drug administered (Table 4, Fig 3).

**Dead Space**

The mean value after nikethamide was lower (P < 0.01) than those after prethcamide + dimenline. Mean values for the last two drugs did not
Table 2—Mean Values of the Parameters Studied, Adjusted for Youden Square.

<table>
<thead>
<tr>
<th></th>
<th>After 6 min.-</th>
<th>After 16 min.-</th>
<th>After 40 min.-</th>
<th>10 min.</th>
<th>20 min.</th>
<th>44 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory Rate (Breaths/min.)</td>
<td>Tidal Volume (ml)</td>
<td>Dead Space (ml)</td>
<td>Minute Ventilation (ml/min.)</td>
<td>Alveolar Ventilation (ml/min.)</td>
<td>VO₂ (ml/min.)</td>
</tr>
<tr>
<td>Prethcamide</td>
<td>21.50</td>
<td>21.46</td>
<td>22.29</td>
<td>22.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikethamide</td>
<td>20.02</td>
<td>21.75</td>
<td>23.31</td>
<td>21.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimeline</td>
<td>22.31</td>
<td>21.33</td>
<td>21.27</td>
<td>21.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prethcamide</td>
<td>541.26</td>
<td>531.10</td>
<td>560.60</td>
<td>531.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikethamide</td>
<td>491.18</td>
<td>517.68</td>
<td>504.85</td>
<td>530.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimeline</td>
<td>461.12</td>
<td>519.04</td>
<td>546.87</td>
<td>544.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Differ significantly. The mean values at the four different times considered did not differ significantly no matter what the drug.

**Alveolar Ventilation**

The mean value after nikethamide was significantly higher ($P < 0.01$) than those after the two other drugs. Again, the latter mean values did not differ significantly. The mean values at each time, independent of the drug administered, showed a progressive linear increase ($P < 0.001$).

**CO₂ Output**

The CO₂ output mean values behaved in similar fashion to alveolar ventilation mean values.

**PaCO₂**

The PaCO₂ mean value after nikethamide was lower ($P < 0.05$) than those after the other two drugs, and the mean values of these last did not differ significantly. PaCO₂ mean values at the four different times showed a linear decrease ($P < 0.001$).

**Side Effects**

A short period of general or local itching, burning sensations, and mild anxiety was present in every patient after the infusion of the three drugs. More severe side-effects (gasing, neuromuscular excitation, emesis, or moderate anxiety) followed prethcamide in eight patients, dimeflune in six patients,
and nikethamide in two patients. No reaction was so severe that the test had to be terminated, and it was possible to complete all observations.

**DISCUSSION**

Although respiratory stimulants are widely used clinically, particularly in Europe, their value in treatment of respiratory failure has not been critically assessed. Though their clinical value in cases of acute external hypoventilation appears to be accepted,\textsuperscript{6,14} and the results of some clinical studies\textsuperscript{1,5,6} indeed suggest a salutary effect, review of their general use in respiratory failure is disappointing.\textsuperscript{11,12}

Jain et al\textsuperscript{5} found that 85 per cent of patients responded to a single intravenous injection of prethcamide with increased minute ventilation, decreased carbon dioxide tension, and increased arterial blood oxygenation. These changes were too small and transient to be clinically useful. Muiesan et al\textsuperscript{9} found that the increased minute ventilation induced by a single intravenous injection of different respiratory stimulants was chiefly a consequence of an increased respiratory rate and only in a small measure of an increased tidal volume. Using different methods, other investigators\textsuperscript{4,6,9,10,15,18} studied the acute effects of these agents and reported a fall in arterial Po\textsubscript{2}, a transient increase in oxygen saturation, and an increase in alveolar ventilation. It was also found that oxygen consumption increased more than carbon dioxide output.\textsuperscript{17,18} Thus, respiratory stimulation increased ventilation only at the cost of greatly increased work of breathing, and the balance between increased oxygen requirement and CO\textsubscript{2} production of respiratory muscles was unfavorable.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Mean values relative to dead space (DS), alveolar ventilation (VA), carbon dioxide output (VCO\textsubscript{2}) and P\textsubscript{a}CO\textsubscript{2} at times O, I, II and III.
Greater effectiveness of some respiratory stimulants has been claimed, but our prior controlled trial of intravenous injection of three agents failed to show any substantial difference of action on the parameters of external ventilation. In the present study, minute ventilation failed to increase significantly after slow intravenous infusion of these same drugs. Also, arterial oxygen tension and pH did not show significant improvement. Alveolar ventilation and CO₂ output were slightly but significantly increased in all patients regardless of the drugs used. Concomitantly, minor decreases in PaCO₂ occurred.

While our results on PaCO₂ alveolar ventilation, and minute ventilation agree, in general, with those reported by others, it is important to note that improvement in respiratory and blood gas data was transient and slight. Though CO₂ and alveolar ventilation increased, the reduction in PaCO₂ and the increase in PaO₂ was very small. As a consequence of the shortness of action of the drugs tested and the relatively slow rate of adjustment of body stores of carbon dioxide, it is likely that the change in arterial PaO₂ due to hyper-ventilation is inadequate. Moreover, the effects of respiratory stimulation on ventilation, carbon dioxide elimination, and arterial oxygenation are all conditioned by the fact that increasing minute ventilation results in lowering the alveolar PaO₂ only to a certain minimum value. Beyond that point, further increments in ventilation lead to an increase in carbon dioxide production by the respiratory muscles at a faster rate than elimination by alveolar ventilation. Simultaneously, oxygen cost of breathing rises. Oxygen consumption and carbon dioxide production will also increase as a consequence of restlessness and increased motor activity induced in most subjects by doses sufficient to increase pulmonary ventilation. An increase in the cost of dissipating carbon dioxide has been reported in patients receiving dichlorphenamide. Similarly it has been suggested that ethamivan may increase tissue anoxia and hypercapnia despite apparent improvement in blood gases. These factors, together with increased work of breathing, certainly nullify the short-lived effects of these drugs on ventilation, even in patients with minimal airway obstruction and when increased minute ventilation is inadequate.
followed by augmented alveolar ventilation. In some of our cases increased minute ventilation was accompanied by an augmentation of physiological dead space so that alveolar ventilation was not changed. Finally, our data indicate that the margin between therapeutic and toxic doses of these agents is sufficiently narrow to preclude their general use.

Though documentation is lacking, it is theoretically possible that hyperventilation secondary to respiratory stimulation could improve distribution of alveolar ventilation and perfusion in a fashion similar to that described by Briscoe et al. and by Emmanuel et al. during voluntary hyperventilation, intermittent positive breathing, and exercise. Further investigation is obviously necessary to clarify this point.

Despite claims to the contrary, the results of this critical and controlled study of the effects of different respiratory stimulants in chronic respiratory failure did not document changes in action or efficacy. The short duration of action, only minimal improvement of alveolar ventilation and blood gases, and high incidence of undesirable side effects suggest that their use in management of chronic respiratory failure cannot be recommended.

APPENDIX

The problem of an experimental design in which there are more treatments than can be accommodated in one block and in which all comparisons are equally important, has been almost completely solved by the introduction of an incomplete block design. One type of this kind of design is known as balanced incomplete block design, for which treatments are arranged in b blocks of k experimental units, each treatment occurring r times altogether, and any two treatments occurring together in block exactly λ times. The mathematical model for the observation Yij1i1 belonging to the ai1 treatment, in the bth block within the ith replication is:

\[ y_{ij1i1} = \mu + \alpha_i + \beta_j + \gamma_{id} + \epsilon_{ij1i1} \]

where \( \mu \) represents the general mean, \( \alpha_i \), \( \beta_j \), \( \gamma_{id} \), and \( \epsilon_{ij1i1} \) the effect of the mean, the replicate, the incomplete block, the treatment and the intrablock error. These parameters are subject to usual restrictions in a linear model for a variance analysis. As all treatments are not used in every block, the treatment means and variances must be adjusted for the effect of the blocks.

Within the frame of the balanced incomplete block design, one of the most characteristic is the Youden square design. Although the shape of a Youden square is rectangular, the name derives from the original method of its construction, as it resembles usually a Latin square without a row or a column. As the Latin square, the Youden square possesses the typical "double control": first with respect to the blocks (rows), because it has all the properties of a balanced incomplete block design, and secondly with respect to the columns, because it is balanced, each treatment appearing once and only once within each of the columns (Fig 1 in the text). The mathematical model for the balanced incomplete block design must be therefore modified as follows:

\[ y_{ij1de} = \mu + \alpha_i + \beta_j + \gamma_{id} + \delta_{de} + \epsilon_{ij1de} \]

where γ represents the effect of the column \( d_{de} \) in the \( b_{de} \) replication.

An incomplete block design type Youden square was used in this study, in order to overtake the difficulty inherent in repeating the test in the same subject with all three drugs. The row, representing a subject, corresponds to a block, incomplete because it has only two out of three drugs; the column represents the order in which the drugs are administered to a subject. The design is thus balanced with respect both to rows and columns, thus making it possible to increase the accuracy of the experiment controlling both sources of variability, rows and columns, i.e., patients and days of testing, and eliminating them from the experimental error.

The basic Youden square used in this study, with \( t = 3 \), \( k = r = 2 \), has been repeated \( n = 6 \) times in order to increase the number of observations per treatment from \( r \) to \( n \mu = 13 \). Thus, the analysis of variance has the following form:

\[
\begin{array}{c|c|c}
\text{Source} & \text{df} & \text{MS} \\
\hline
\text{Columns} & (kn-1) & \\
\text{Blocks (adjusted)} & (n-1) (t-1) & \\
\text{component (a)} & (t-1) & \\
\text{component (b)} & (t-1) & \\
\text{Block total} & n (t-1) & E_b \\
\text{Treatments} & (t-1) & \\
\text{(unadjusted)} & (t-1) & E_b \\
\text{Error} & (t-1) (nk-n-1) & E_e \\
\hline
\text{Total} & (ukt-1) & \\
\end{array}
\]

where \( k \) is the number of experimental units per block, \( t \) the number of treatments and \( n \) the number of repetitions of the basic design.

Furthermore, it is important in this study to observe the comparative effect of three drugs at different times, say time 0, 1, 2, and 3, according to a factorial arrangement with two factors, i.e., drug and time, the first at three levels and the second at four levels. Therefore, in the Youden square design the effect of time is superimposed in a factorial arrangement and the analysis of variance is modified as follows:

\[
\begin{array}{c|c|c}
\text{Source} & \text{df} & \text{MS} \\
\hline
\text{Columns} & (kn-1) & \\
\text{Blocks (adjusted)} & (n-1) (t-1) & \\
\text{component (a)} & (t-1) & \\
\text{component (b)} & (t-1) & \\
\text{Block total} & n (t-1) & E_b \\
\text{Treatments} & (t-1) & \\
\text{Times} & (a-1) & \\
\text{Interaction treatments} & (t-1) (a-1) & \\
\text{x times} & & \\
\text{Group total} & (at-1) & \\
\text{(unadjusted)} & & \\
\text{Error} & (at-1) (nk-n-1)-1 & E_e \\
\hline
\text{Total} & (ankt-1) & \\
\end{array}
\]

where \( a \) represents the effect of the time.

For the statistical analysis, the total sum of squares (s.s.), the s.s. for columns and the s.s. for groups, are found by the usual methods. The s.s. for blocks (adjusted for treatments) is in effect the s.s. within Youden square; it is composed by component (a) corresponding to a sum of the rows x columns interactions over all \( n \) Youden squares, and component (b) corresponding to a s.s. of the quantities \( W = \)
(t-k)T-(t-1) B, + (k-1)C, divided by n(k)(t-k) (k-1), where T represents the treatment totals, B, for each treatment the total of all the blocks which contain the treatment and G the grand total. The error s.s. is found by subtraction. To examine within the (at-1) group the effect of the (t-1) treatments, of the (a-1) times and of the (t-1) (a-1) interaction treatment x times, it is necessary to adjust the total for any treatment according to the formula:

treatment total adjusted = T + μW

where μ is an adjustment factor equal to

μ = n(E0 - E) / n((k-1)E0 - (t-k) (n-1)E)

The adjustment factor for any single observation within each treatment is done by μW/akn. With these adjusted values it is possible to find the s.s. for treatments, for drugs and for treatment x drug interactions by the usual methods.

The estimate for the treatment effects is thus adjusted for blocks, but no adjustment is needed for the estimate of the interaction.

For the F test it is not possible to test against the E, since this error mean square contains some blocks effects. The E, must be increased to E' = E, (1+i) in order to take account of sampling errors in the block correction values μW.

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