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for a single 15-minute period of infusion is as follows:

\[ \text{Patient's weight in lb.} \div 25 = \text{milliliters of a 25 percent nikethamide solution.} \]

For the preparation of one complete course, multiply this amount by seven, then empty a 500 ml bottle of five percent dextrose in water so that when nikethamide is added, the total amount of solution will equal 350 ml. Give 50 ml of this solution over 15 minutes at two hour intervals. The procedure is further simplified by the use of a pediatric intravenous set.

Give continuous oxygen by nasal catheter, nasal cannulae, Edinburgh mask or Venturi mask.

Example

Man weighing 150 pounds.

Single nikethamide dose = \( \frac{150}{25} = 6 \) ml.

Seven doses = \( 7 \times 6 = 42 \) ml.

Empty 500 ml bottle of five percent dextrose in water until it contains 308 ml. Add 42 ml of nikethamide. Total volume is now 350 ml. Give 50 ml over 15 minutes at two hour intervals.

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The Case Against the Use of Respiratory Stimulants*

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"I don't see no p'ints about that frog that's any better'n any other frog." — Mark Twain

Management of the patient with chronic obstructive pulmonary disease in respiratory failure has involved the use of many procedures including a variety of drugs which are designed to beneficially reverse the pathophysiologic alterations found in respiratory failure, namely: hypoxemia, hypercapnia, and acidemia. There is no argument with the statement that emergency treatment "never cured anything" but is necessary "to buy the time" for more definitive therapy. Because of the poor prognosis and the emergency nature of the medical situation, however, most of these patients are treated by a number of therapeutic measures simultaneously and the effect of any one procedure cannot be adequately evaluated. This is especially true for the respiratory stimulants where suitably controlled clinical trials are sadly lacking.

Respiratory failure is the final common pathway of the various physiologic defects encountered in chronic obstructive pulmonary disease. These in-clude increased airway resistance, abnormal distribution of inspired air, relative alveolar hypoventilation and increased venous admixture due to altered ventilation/perfusion relationships and diminished elastic recoil resulting in an increased work of breathing. The success or failure in treatment depends, in large measure, on whether these defects are due to reversible bronchitis or irreversible alveolar destruction. ¹

Considerable attention has been given to the detrimental effects of severe hypoxemia including increase in pulmonary arteriolar resistance, ² secondary erythremia, ³ tissue hypoxia with lactic acidosis ⁴ and cardiac arrhythmias. ⁵ Correction of these abnormalities by the administration of oxygen and the dangers of improper use of oxygen have received equal attention. ⁶⁻¹⁰ Barach ¹¹⁻¹² was the first to report mental confusion and coma in patients with severe pulmonary emphysema receiving oxygen therapy and recommended the use of a graded oxygen program employing low concentrations. Subsequently, Campbell ¹²⁻¹⁴ designed a Venturi mask which provided a more precise control of the oxygen concentration delivered in the low ranges, 24 to 40 percent. A number of clinical studies ¹⁵⁻¹⁷ have confirmed the value of controlled oxygen therapy in acute respiratory failure in chronic obstructive pulmonary disease. In the majority of instances, an arterial oxygen tension of 50 mm Hg or higher was obtained with minimal

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changes in PaCO₂ or pH. Mitroofer, Karetksy and Mead,18 however, reported wide variations in arterial oxygen tension with the use of the Venturi mask at known concentrations of inspired oxygen in patients with pulmonary insufficiency and emphasized the need for frequent monitoring of the arterial blood gases.

Hypercapnia reflects a state of alveolar hypoventilation. Following the demonstration by Alexander and co-workers19 that patients with chronic obstructive pulmonary disease and hypercapnia had a diminished ventilatory response to inhaled carbon dioxide implicating a reduction in sensitivity of the respiratory center, other authors20-21 presented evidence that hypercapnia was secondary to the increased mechanical work of breathing. Wilso and associates22 showed that voluntary hyperventilation only minimally lowered the PaCO₂ in patients with chronic obstructive disease. These findings were confirmed and extended by Gilbert et al22 who found that voluntary hyperventilation was ineffective in lowering arterial CO₂ tension and often resulted in an increased PaCO₂ which was especially true during exercise. They concluded that hypercapnia in patients with chronic obstructive pulmonary disease is not due to overall underventilation, but that these patients are unable to maintain an effective increase in ventilation without excessive deadspace ventilation or without an excessive increase in the carbon dioxide production by the respiratory muscles. In this connection, it is of interest that Riley24 postulated that in severe airway obstruction, the increase in the production of carbon dioxide by the muscles of respiration is faster on a percentile basis than the increase in alveolar ventilation.

A number of papers24-26 have emphasized the important role of hypercapnia with respiratory acidosis as an adaptive mechanism permitting the elimination of large amounts of carbon dioxide per breath and thus enabling the patient to tolerate an increase in the work of breathing which would otherwise be intolerable. Since hypercapnia serves as an adaptive mechanism in chronic obstructive pulmonary disease, its correction by appropriate therapy is not as urgent as for hypoxemia.

Acidemia results in a shift in the oxyhemoglobin saturation curve to the right, produces pulmonary vasoconstriction and bronchoconstriction accentuating disturbances in ventilation/perfusion ratio, and with hypercapnia causes cerebral vasodilatation. As with hypercapnia, correction of acidemia is of secondary importance to hypoxemia provided the pH does not fall below an acceptable level of 7.25.13

Having defined the major pathophysiologic factors encountered in acute respiratory failure in chronic obstructive pulmonary disease, the question is whether the "respiratory stimulants" can effectively improve arterial oxygen tension, lower the elevated carbon dioxide tension and correct acidemia. Even if these objectives cannot be realized, can they prevent further deterioration in the seriously ill, unconscious or uncooperative patient who would otherwise require ventilatory assistance following the establishment of an adequate airway?

Pharmacologically, there are no specific respiratory stimulants. These compounds, represented by such drugs as nikethamide (Coramine), ethamivan (Emivan), pentyleenetrazol (Metrazol) pethracamide (Micoren), dimeline amphetamine and picrotoxin are powerful central nervous system stimulants referred to as analeptic agents.25 These drugs were initially developed as "arousal" agents, particularly in states of central nervous system depression due to barbiturate intoxication and to facilitate recovery from postanesthetic depression. While the effect of these agents in such states cannot be compared with their usefulness in respiratory failure due to chronic lung disease, it is of interest that these drugs have been generally discarded for the treatment of barbiturate poisoning where the end organ, the lung, was presumed to be healthy.26-28 "Mortality rate was 25 percent during the period of analgetic therapy, and 2 percent or less during the following 12 years. During this last period, tracheal intubation with or without artificial ventilation was substituted for analeptics as treatment for barbiturate intoxication."29

The marked variations in sensitivity to the respiratory stimulants due in part to individual variability and to the level of central depression, makes it difficult to avoid adverse reactions. Gaensler and Graham31 state that there is practically no respiratory stimulation until the onset of convulsions, and that nikethamide has been more widely used because it is one of the least "effective" members of this group.

There are a number of studies3-12 which demonstrate that patients in mild to moderate respiratory failure and, in some instances, severe failure who are conscious can be adequately treated by conservative measures including controlled oxygen therapy, bronchodilators, and measures to facilitate bronchial drainage together with frequent monitoring of the arterial blood gases and pH. With this approach an acute mortality rate as low as 12 percent has recently been reported.14 The major problem is with the unconscious or uncooperative patient whose condition is deteriorating despite...
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Conservative measures. The value of respiratory stimulants in this type of patient requires assessment of their effect on:

1. Hypoxemia. Cherniack and Young found a rise in oxygen consumption during ethamivan administration which was due to general muscular activity and could not be attributed to increase in ventilation. Because of the increase in metabolism, arterial oxygen tensions actually deteriorated. Negligible changes in oxygen tensions have been reported by other investigators. It has been suggested that oxygen should be administered during stimulant therapy to increase arterial oxygen tension and to make up for the increase in oxygen consumption. Since the effect of the respiratory stimulants is brief, lasting from one to five minutes following intravenous administration, and the method proposed by Woold involves the administration over a 15 minute period every two hours, there is real danger of producing "peaks and valleys" in the oxygen available to the tissues. Campbell has emphasized the hazards of intermittent oxygen therapy and even though oxygen is being administered continually, changing demands by the tissues would have an effect similar to "interruption" delivery.

2. Hyperpnea and Acidemia. The effect of respiratory stimulants on carbon dioxide tension and acidemia has been variable. Several reports have reported decreases in some patients while others have found either no change or an actual increase in arterial carbon dioxide tensions. One favorable report states that patients with the highest PaCO\textsubscript{2} show the least response. This would be in keeping with the concept that patients with the more marked disturbances in ventilatory function would be less able to respond to stimulants. Patients with chronic obstructive pulmonary disease have a marked increase in the work of breathing. Physiologic changes impose mechanical limitations to the ability of the lung to respond to the need for augmented ventilation. In respiratory failure this response fails and any increase in ventilation by stimulants may increase carbon dioxide production beyond the capacity for its elimination. This has been likened to "whipping a tired horse."

In reviewing the literature, there appears to be one indication for the use of respiratory stimulants with which most investigators are in agreement: where respiratory failure has been precipitated or aggravated in a patient with chronic obstructive pulmonary disease by the injudicious use of oxygen or hypnotics. In general, the evidence would support the opinion expressed by Basder and Basder in their editorial that rational therapy as recommended by the Committee on Therapy of the American Thoracic Society still calls for the use of various measures designed to: 1) improve oxygenation by controlled administration; 2) reduce the work of breathing through the appropriate use of bronchodilators, expectorants, chest physiotherapy and steroids in selected cases; 3) properly timed use of antibiotics, and 4) ventilatory assistance with the maintenance of a patent airway.

From time to time, a new analeptic is developed which is said to be a specific "respiratory stimulant." Initial reports are enthusiastic, but when subjected to more critical appraisal, usage is discontinued or at best reserved for a very limited or special situation by a few remaining investigators. Where sound physiologic principles dictate, it would be well if we could "bury" such controversial agents whose potential for harm due to inherent toxicity or resulting in the delay of the application of more appropriate measures, is greater than any benefit as documented by acceptable studies in the literature. Such is the case with "respiratory stimulants."

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