VANILLIC DIETHYLAMIDE (ETHAMIVAN) AND THE HYPOVENTILATION SYNDROME IN THORACIC SURGERY

JEAN-PAUL DECHÊNE, M D ^{1b}

THE HYPOVENTILATION SYNDROME with carbon dioxide retention, collection of secretions, and consequent atelectasis is one of the most important postoperative and postanesthetic complications encountered in thoracic surgery, especially that of the lungs. Hence the necessity for the anaesthetist to maintain ventilation not only during the operation proper but also postoperatively. To this end, several means, mechanical as well as chemical, are made available by modern therapy, apart from sound prophylaxis. Such prophylactic treatment consists of the use of an adequate but non-depressant premedication and light anaesthesia which will allow both optimum oxygenation and ventilation. The ventilation may then be measured with a Wright respirometer as the patient is aroused, and if necessary, a Bird intermittent positive pressure apparatus is used for as long as the minute ventilation is not back to near its normal level, that is in the neighbourhood of 6 to 8 litres for an adult, with 400–500 c.c. of tidal air and breathing rate of 16–20 per minute. As normal respiration is restored, the patient is again left to himself but is given oxygen with a NCG or a BLB mask. If ventilation is considered satisfactory by the anaesthetist, the patient is then taken to the intensive care unit, where the same procedure will be repeated if necessary and as often as needed.

Controlled ventilation is administered through a tracheotomy cannula and with an adequate respirator—the Bird or Bennett apparatus in our hospital—for extreme cases of hypoventilation, which is caused, usually, by a major cardiorespiratory insufficiency already present before the operation, particularly in the patient with a pulmonary condition.

I VANILLIC DIETHYLAMIDE (ETHAMIVAN)

1 *Chemistry*

Ethamivan is a white, crystalline, odourless powder comparatively insoluble in water. It melts at 95.5° and its molecular weight is 223.26. Ethamivan is supplied as a 5 per cent diethanolamine aqueous solution for intravenous use and in tablet form for oral use.

2 *Pharmacology*

Respiratory stimulation mediated principally via the medullary centre is the most important pharmacological effect of Ethamivan. Large doses will eventually arouse the chemoreceptors and stop in the medulla the inhibiting impulses coming from higher nervous centres.

^aDepartment of Anaesthesia & Resuscitation, Laval Hospital, Quebec

The drug also exerts an arousing effect through direct stimulation of the cortex. On the average, the respiratory effects of Ethamivan are seen within 30 seconds following an intravenous injection and last for about 10 minutes. Tidal air is increased by 48 per cent and the respiratory rate by 24 per cent.

The depth of breathing is therefore the feature which is most particularly involved. The action of the drug may be maintained with continuous intravenous infusion and by carefully adjusting the drip rate. The effects of the oral form are less pronounced, they are seen between one and four hours after intake depending on individual patient responsiveness.

No serious untoward effects on the blood pressure and cardiovascular system have ever been reported in man when the drug is used in therapeutic doses. Moreover, no tachyphylactic effect has been observed, which means that consecutive doses of intravenous Ethamivan are as effective as the first dose. However, some secondary effects have been reported such as sneezing, coughing, pruritus, agitation, but they can usually be avoided. We shall give a detailed account of these effects when describing the procedure employed.

II OUR TECHNIQUE

This analeptic respiratory medication has been employed by numerous investigators for various causes of central nervous system and respiratory depression. This explains, in our opinion, the variety of techniques resorted to. Ethamivan is being used to treat intoxication of the central nervous system by depressing agents, to promote awakening or lighten general anaesthesia especially for the ambulatory patient, and to prevent or treat the hypoventilation syndrome in the presence of respiratory insufficiency with CO_2 retention, which is seen most often in pulmonary surgery and with the postoperative and postanesthetic sequelae. This syndrome is marked by drowsiness, headache, lethargy, weariness, mental aberration, a period of irascibility and restlessness, tremor of the extremities, tachypnoea with sharply reduced depth of respiration, cardiac decompensation, cyanosis, even apnoea and coma.

In this clinical study we are concerned with the latter indication exclusively. Consequently, a continuous 0.1 per cent intravenous infusion appeared to us to be quite in order since we are dealing with a long-term treatment. Yet, some more serious cases of respiratory insufficiency did require a single injection of Ethamivan before the continuous drip infusion to combat a severe hypoventilation syndrome faster and more effectively. In such cases, a single dose of 100 mg Ethamivan in 20 c.c. of saline is given. This dilution allows a slow injection of the drug with the chief advantage of avoiding the side-effects altogether.

Finally, the oral route is also used after the intravenous infusion to secure a prolonged effect of the adjuvant analeptic medication when the patient can be fed normally, that is 48 hours after the operation on the average. This oral medication is only used when the pulmonary condition of the patient (asthma, chronic bronchitis, emphysema) calls for a prolonged course of treatment of the hypoventilation syndrome, which always remains a possibility in the presence of

such a pathologic condition. For a week or even longer, the patient receives 60 mg tablets, four times a day. The 0.1 per cent continuous infusion technique was the only one used and required, immediately after the operation, to offset the hypoventilation syndrome in 85 per cent of the cases reported here. The cases discussed here were all postoperative patients lacking adequate ventilation. It must also be pointed out that the halothane-ether anaesthetic technique used with our patients permits a prompt and immediate postoperative arousal and that in no circumstance did we have to resort to Ethamivan to spur awakening or reduce anaesthesia.

It appeared that the most effective dose of Ethamivan was between 0.05 and 0.07 mg per kg per minute to provide satisfactory ventilation while averting the side-effects from the drug.

III RESULTS

We have studied the effects of Ethamivan in the treatment of the hypoventilation syndrome in 101 cases of thoracic surgery, particularly surgery of the lungs.

1 *General Review of the Cases Studied*

The patients included in the study are a group of 101 consecutive cases of thoracic surgery treated in our institution from April 1962 to December 1963. These were pulmonary cases for the most part, all of them being affected by the hypoventilation syndrome in various degree. This syndrome was either detected preoperatively in patients whose cardiorespiratory function was notably inadequate, or diagnosed postoperatively through clinical signs of hypoventilation (rapid breathing and drastically reduced depth of respiration), spirometry with deficient minute ventilation (tidal air less than half its normal level), and studies of the arterial blood which indicated respiratory acidosis.

Patients were men and women whose ages were between 16 and 70 years. Their condition (tuberculosis, diaphragmatic hernia, bronchiectasis, and cancer) justified a more or less imperative and urgent thoracic operation. The following shows the type and number of surgical operations performed: 35 lobectomies, 4 pleurectomies, 28 pneumonectomies, 2 partial lobectomies, 2 Shede operations, 8 thoracoplasties, 18 pulmonary biopsies and thoracotomies, 2 diaphragmatic hernias, 1 oesophageal resection, 1 sternochondroplasty.

2 *Discussion*

Most of the cases in the study presented respiratory insufficiency diagnosed preoperatively from a study of their pulmonary function. This is generally true for most surgical procedures performed in cases of established tuberculosis. The eight thoracoplasties and the two Shede operations were necessitated for treatment of bronchopleural fistulae or stubborn cases of empyema associated with pneumonectomies (16 out of 28 tuberculosis cases) where the function is of course drastically reduced.

This is equally true in the treatment of cancer, where owing to neoplastic

involvement the pulmonary function is carried more and more by only one lung. In this series resection was possible in 12 cases of 28 with neoplasm.

The cases of lobectomy (tuberculosis, cancer, and bronchiectasis) were all classified beforehand as having various degrees of respiratory insufficiency because of a serious pulmonary condition such as asthma, chronic bronchitis, and emphysema.

The two cases of diaphragmatic hernia were patients with marked obesity. In such patients postoperative hypoventilation is a common occurrence.

The woman with sternochondroplasty was also stricken with bronchiectasis involving the pulmonary function.

The case of cancerous cardia was a 70-year-old man. Restrictions in gaseous exchange are always more critical in older than in younger adults.

Finally, the four pleurectomies were all performed on young people. Good postoperative ventilation might normally be expected in these, but postoperative recovery proved to be extremely disappointing, from this point of view, because of pains associated with a new spontaneous pneumothorax.

Among the patients reported above, there were a few cases of lobectomy and of partial lobectomy where pulmonary function was not deficient preoperatively. However, this respiratory insufficiency was observed postoperatively for various reasons, such as lack of physiotherapy, marked obesity, restlessness, over-depressing sedation, and it was treated accordingly.

In review, the hypoventilation syndrome was present at different times and in varying degrees in all the cases studied and reported in this paper. The condition was relieved by the administration of intravenous vanillic acid diethylamide by continuous infusion.

3 *Specific Advantages*

The use of respiratory analeptics has often given rise to heated argument in the field of postanesthetic resuscitation. We are convinced that Ethamivan given by continuous infusion to cases of hypoventilation syndrome has been highly beneficial to our patients. It improved their postoperative ventilation and avoided in them a postoperative tracheotomy, which is always a risky surgical procedure that should be abstained from if at all possible. Nevertheless, this drug used alone does not provide an over-all means for treating *all* cases of respiratory depression efficiently. At no time should it be substituted for the basic prophylactic and therapeutic measures afforded by sound anaesthesia and resuscitation. On the other hand, we think that it may be definitely valuable when properly used in conjunction with other therapeutic measures for respiratory depression such as manual or mechanical intermittent positive pressure.

We feel that other observers have been right in calling vanillic acid diethylamide a chemical respirator and the least that can be said about it is that it represents a new method of combating the hypoventilation syndrome more effectively. This method proved to be very efficient as we used it with our patients, and the incidence of pulmonary involvement due to hypoventilation was reduced to a minimum. In fact, only a few catheter aspirations of the trachea were required, and no tracheotomies were found necessary postoperatively. The routine

use of this intravenous "chemical respirator" was undoubtedly instrumental in making the postoperative intensive care of our patients more simple

In summary, there is certainly a place for the use of a continuous intravenous infusion of vanillic diethylamide (Ethamivan) in the modern treatment of the hypoventilation syndrome in thoracic surgery, and if this technique is applicable in pulmonary surgery it perhaps merits a more general clinical trial in general surgery, where occasionally pulmonary pathology makes the hypoventilation syndrome a problem in the postoperative period. Ethamivan is therefore another tool put at the disposal of the clinician by modern therapeutics for the ventilation of his patient

RÉSUMÉ

L'emploi d'analeptiques respiratoires a souvent été l'objet de sérieuses controverses en anesthésie-réanimation. Pour notre part, dans plusieurs cas atteints du syndrome d'hypoventilation, nous avons jugé que l'emploi "d'Ethamivan," en perfusion intra-veineuse continue, a rendu de grands services à nos malades et leur a permis de mieux se ventiler post-opératoirement, tout en évitant à l'occasion une trachéotomie post-opératoire qui demeure toujours une chirurgie délicate à éviter si possible. Nous restons cependant convaincu que cette médication seule n'est pas une thérapeutique universelle pour traiter efficacement toutes les dépressions respiratoires rencontrées en médecine. Elle ne doit en aucune façon nous faire oublier les mesures prophylactiques et thérapeutiques de base d'une bonne anesthésie-réanimation. Mais par ailleurs, nous croyons qu'elle peut définitivement rendre service, si elle est associée à bon escient aux autres thérapeutiques de la dépression respiratoire par exemple à la P P I manuelle ou mécanique.

A notre opinion, le diéthyl-amide vanillique a été surnommé avec raison par les auteurs le respirateur chimique de la ventilation et le moins qu'on puisse dire à son sujet c'est qu'il représente une méthode nouvelle de lutter plus efficacement contre le syndrome d'hypoventilation. Entre nos mains du moins, la méthode s'est avérée très efficace et l'incidence des complications pulmonaires propres à l'hypoventilation a été réduite au minimum chez nos malades. En effet seulement quelques aspirations trachéales au cathéter ont été rendues nécessaires et aucune trachéotomie a dû être pratiquée dans les suites opératoires de ces derniers. C'est donc dire que l'emploi continu de ce "respirateur chimique" par voie intra-veineuse a certainement contribué à simplifier les soins intensifs de nos malades à la période postopératoire.

En résumé dans le traitement moderne du syndrome d'hypoventilation en chirurgie thoracique, il y a certainement place pour l'usage par voie intra-veineuse d'une perfusion continue de diéthyl-amide vanillique commercialisé sous le nom "d'Ethamivan." Et si cette technique est applicable avec succès en chirurgie pulmonaire, elle mérite peut-être un essai clinique plus généralisé en chirurgie générale où à l'occasion une pathologie pulmonaire fait craindre à la période post-opératoire la présence de ce syndrome d'hypoventilation. Avec "Ethamivan" c'est donc une arme de plus que la thérapeutique moderne met à la disposition du clinicien pour la bonne ventilation de son malade.

REFERENCES

1. ARANOVITCH, M , KAHANA, L M , MEAKINS, J F , PLACE, R E G , & LAING, R Vanillic Diethylamide in the Management of Acute Respiratory Insufficiency A Preliminary Report Canad M A J 85 875 (1961)
2. COTTRELL, R F & STOELTING, V Pulmonary Function Test in the Immediate Postoperative Period Med Times (April 1961)
3. MILLER, M J , HAND, B M , & CRELLIN, J A Pharmacologic Effects of Intravenous Vanillic Acid Diethylamide in Man Clin Pharmacol & Therap 2 689 (1961)
4. MILLER, W F , ARCHER, R K , TAYLOR, H F , & OSSENFORT, W F Severe Respiratory Depression J A M A 180 805 (1962)
5. ROMAGNOLI, A & DIAMOND, M J Some Trials with Vanillic Diethylamide A New Analeptic Canad Anaesth Soc J 8 551 (1961)
6. SILIPO, S , HAGEDORN, C , ROSENSTEIN, I N , & BAUM, G L Experiences with Ethamivan, a New Respiratory Stimulant and Analeptic Agent J A M A (1961)
7. SLATER, H M The Use of Vanillic Acid Diethylamide following Anesth & Analg 41 (1962)