EFFECTS OF AMINOPHYLLINE, NIKETHAMIDE, AND SODIUM SALICYLATE IN RESPIRATORY FAILURE

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The treatment of acute respiratory infections in patients with chronic lung disease remains unsatisfactory. Despite the use of antibiotics, oxygen, and bronchodilators, many die of respiratory failure, and the mortality from "bronchitis" in England and Wales has remained virtually unchanged over the past 14 years (Registrar-General's *Statistical Review*, 1942-55). Relief of anoxia is essential in the management of acute exacerbations of bronchitis, but the continuous administration of oxygen in high concentration may lead to fatal respiratory acidosis due to inadequate ventilation resulting from removal of the anoxic stimulus to breathing (Westlake, Simpson, and Kaye, 1955; Sieker and Hickam, 1956).

The most rational method of treating this complication is by artificial ventilation. However, these patients are much more difficult to ventilate artificially than those with respiratory failure due to muscular paralysis whose lungs are healthy. Moreover, large numbers of patients with ventilatory failure due to chronic lung disease are treated in hospitals which do not at present have the resources of apparatus and personnel required for maintaining artificial ventilation over long periods of time. We therefore planned to investigate the possibility of increasing ventilation by chemical stimulation. As a first step the following investigation was carried out to screen three drugs which are reputed to be respiratory stimulants to see if they justified more detailed trial in the management of these patients.

Methods

Fourteen studies were carried out on 11 patients with chronic bronchitis and emphysema admitted to the Middlesex Hospital during the winter of 1955-6. All had superimposed acute respiratory infections and most had ventilatory failure with arterial carbon dioxide tensions greater than 50 mm. Hg (see Table). The effectiveness of the three drugs as respiratory stimulants was assessed by following changes in the level of arterial pCO_2 . Samples of blood were obtained from an indwelling arterial needle inserted into the brachial artery and were analysed for plasma CO_2 content, pH, and pCO_2 as previously described (Westlake, 1954). As controls, three samples were withdrawn at intervals of 10 to 15 minutes before the administration of the drug. The patients were breathing air. The subsequent procedure varied with the drug used and the response of the patients.

Aminophylline. 0.5 g. (20 ml. of aminophylline injection B.P.), was injected intravenously in three to four minutes. A further 0.5 g. was infused in 300 ml. of 5% glucose for a further 30 minutes. Arterial blood samples were taken 15 and 30 minutes after the first

0.5 g. had been injected. Further samples were not taken, because in none of the subjects was there a significant response.

Salicylate.—8 g. of sodium salicylate in 300 ml. of 5% glucose was injected intravenously over a period of one hour. Three to five arterial samples were taken at intervals up to four hours after completion of the infusion.

Nikethamide.—The dose and rate of administration of nikethamide had to be varied from patient to patient because there was a marked variation in their sensitivity. The general plan was to inject 0.25 g. (1 ml. of nikethamide injection B.P.) intravenously at intervals of one minute until a response was obtained or the patient complained of excessive side-effects (itching, paraesthesiae, heat, breathlessness, nausea). Further quantities were then injected to try to maintain the respiratory stimulation for 30 minutes. Two or three arterial samples were taken during this period and a further one 10 minutes after the infusion was completed. No further samples were taken, because the stimulant effect had ceased by this time.

Results

The results are summarized in the Table and the Chart. It should be noted that changes of less than 3 mm. Hg are within the range of experimental error and are, moreover, of little clinical importance.

Summary of Results

Case No.	Age and Sex	Mean Art. pCO ₂ mm. Hg		Mean Art. pH		
		Before	During and After	Before	During and After	
<i>Aminophylline, 1 g. i.v. in 30 mins.</i>						
1	68 F	63.5	63	7.40	7.41	
2	53 M	85.5	84	7.30	7.31	
3	76 F	44.5	43.0	7.55	7.56	
4	49 M	83.5	78.5	7.28	7.30	
5	58 M	61.5	60.5	7.36	7.37	
6	60 F	65.5	64.5	7.38	7.39	
<i>Sodium Salicylate, 8 g. i.v. in 1 hour</i>						
1	68 F	56	47	7.47	7.52	*45 mg./100 ml.
4	49 M	81	77	7.33	7.36	*35 "
7	62 M	63	53	7.36	7.44	*48 "
<i>Nikethamide</i>						
4	49 M	65.5	58.0	7.38	7.44	Quantity Administered
8	49 M	48.0	46.0	7.41	7.42	6.25 g. in 40 mins.
9	60 F	49.0	48.5	7.43	7.43	4.0 " " 16 "
10	53 M	71.5	58.5	7.36	7.40	2.5 " " 20 "
11	70 M	60.5	51.5	7.43	7.48	5.25 " " 35 "
						2.5 " " 12 "

* Plasma salicylate concentration 30-60 minutes after administration.

Aminophylline.—In only one patient was there a significant fall in pCO_2 , and that was not large (5 mm.). Three of the patients complained of feeling warm and of palpitation.

Salicylate.—All the subjects showed a fall in pCO_2 , which persisted until the end of the period of observation (two hours in one subject; four hours in the others). Mild salicylism (tinnitus and deafness) occurred in all the subjects for 6 to 12 hours. The plasma salicylate concentration varied between 34 and 53 mg. per 100 ml.

Nikethamide.—The two subjects (8 and 9) with the lowest initial CO_2 tensions showed no respiratory response. There was obvious stimulation of the breathing in the other three and the arterial CO_2 tensions fell. The respiratory stimulation ceased within five minutes of discontinuing the drug.

*Dr. E. K. Westlake died on June 18, 1958.

Discussion

Ideally, a drug for use as a respiratory stimulant in these patients should have the following properties: it should be able to stimulate the breathing even when it is depressed by O_2 ; there should be no increase in metabolism causing increased O_2 consumption and CO_2 production; there should be minimal stimulation of the central nervous system other than the respiratory centres; the response should be sufficiently prompt, so that ventilation can be regulated by adjusting the rate of administration without delayed response or excessive persistence if the effect is undesirable; the dose required by an individual patient should not be too critical, because this involves frequent alteration of the rate of administration. None of the three drugs satisfied these requirements, but nikethamide seemed to offer more promise than the others.

The value of a drug as a respiratory stimulant in these patients can be assessed only by measuring the arterial pCO_2 . Measurements of total ventilation or of respiratory rate will detect respiratory stimulation, but if the work of breathing is greatly increased or if the metabolic rate is increased the production of CO_2 may be greater than the extra excretion. The arterial CO_2 tension may then rise. We have, in fact, observed this in a patient whose respiratory effort was increased by nikethamide but whose arterial CO_2 tension rose from 120 to 150 mm. Hg. In spite of the administration of O_2 he was very cyanosed, and at necropsy the major bronchi were largely occluded by tenacious sputum. Respiratory stimulants are unlikely to be of benefit to such a patient.

AMINOPHYLLINE . SALICYLATE . NIKETHAMIDE.

Arterial pCO_2 before and after administration of aminophylline, salicylate, and nikethamide. The vertical lines indicate (A) the range of the control readings; (B) the range of the readings during or after administration of the drug. The horizontal or sloping lines join the mean values.

Aminophylline.—There is good evidence (Wechsler, Kleiss, and Kety, 1950; Stroud *et al.*, 1955) that aminophylline has a respiratory stimulant action in normal individuals. The results we have obtained in patients with respiratory failure due to chronic lung disease are not encouraging, although we gave larger amounts of the drug than are usually administered. Galdston and Geller (1957), however, have reported that aminophylline (0.5 g. initially, followed by 100 mg. hourly, intravenously) counteracts the respiratory depression which O_2 administration causes in patients with chronic lung disease.

Salicylate.—Wégria, Capeci, Kiss, Glaviano, Keating, and Hilton (1955) have shown that similar doses of sodium salicylate reduce the arterial pCO_2 in patients with respiratory failure due to chronic lung disease. Our results confirm these findings. Samet, Rosenthal, and Bernstein (1958), however, did not observe any respiratory response to smaller doses of salicylate. Further evidence is required before salicylates can be recommended for routine use. Firstly, the doses used have been very large; secondly, the other effects of salicylates, notably the increase in metabolic rate (Tenney and Miller, 1955), are undesirable in these patients; and, thirdly, the action of salicylates is very prolonged, and if the response is undesirable it cannot be counteracted.

Nikethamide has been used for many years as a respiratory stimulant. We have previously used it in the treatment of CO_2 narcosis, when it awakens the patient and has the additional beneficial effect of causing coughing. The dose required is, however, much greater than that usually recommended. Our results show that a considerable fall in the arterial pCO_2 can be produced and that the duration of action is short. We therefore decided to investigate it further.

FURTHER STUDIES, USING NIKETHAMIDE

Nikethamide having been chosen, the next step was to see if it could be used to maintain ventilation in patients with respiratory depression due to O_2 administration.

In this study the arterial CO_2 and O_2 tensions were measured by the method of Riley (Riley, Campbell, and Shepard, 1957). Two patients were studied.

Case 1

A man aged 59, with chronic bronchitis, emphysema, funnel deformity of the sternum, acute purulent bronchitis, and heart failure, deteriorated during the first four days in hospital. He was very anoxic, but the administration of O_2 caused unconsciousness and muscular twitching. On the fourth day of admission his arterial pCO_2 was 65 mm. Hg and O_2 saturation 65%. The administration of O_2 (7 l./min. by oronasal mask) causing the pCO_2 to rise to 97 mm. Hg, and he became unconscious. A continuous intravenous infusion of nikethamide in 5% dextrose was given for 30 hours, during which time the arterial pCO_2 ranged between 61 and 71 mm. Hg. His arterial O_2 saturation was 100% throughout. The rate of administration of nikethamide varied between 20 and 40 mg./min. At any given time it was critical in that a reduction of 2-4 mg./min. allowed him to relapse into narcosis, whereas a corresponding increase caused considerable distress due to itching, paraesthesia, and intense dyspnoea with a respiratory rate of 60/min. After 30 hours it was found possible to discontinue first the nikethamide and then the O_2 , and his arterial pCO_2 eventually settled to 49-52 mm. Hg, with an arterial O_2 saturation of 81-85%.

Case 2

A man of 62, with chronic bronchitis, emphysema, bronchopneumonia, and slight heart failure, deteriorated during the first three days in hospital. He was severely anoxic, but the administration of O₂, either intermittently or continuously, at low flow rates (1-3 l./min.), caused CO₂ narcosis. When he was breathing air his arterial pCO₂ was 74 mm. Hg and O₂ saturation 39%. The administration of O₂ at 7 l./min. by oronasal mask caused the pCO₂ to rise to 140 mm. Hg. A continuous intravenous infusion of 2% nikethamide in 5% glucose was started. There was no clinical response until the rate of administration was raised to 80 mg./min. for 1½ hours. At this time he became fully conscious, coughed up copious quantities of sputum, and became very breathless. Subsequently consciousness was maintained and the arterial CO₂ tension was reduced to 85-90 mm. Hg by a rate of administration of 36-48 mg./min. Attempts to decrease the rate of administration caused unconsciousness, with slow shallow breathing. Stopping the O₂ caused intense cyanosis. Ventilation was maintained with nikethamide in the above dosage for 24 hours, and his clinical condition was satisfactory. He then became unconscious and his breathing became slower and shallower. The arterial pCO₂ rose to 120 mm. Hg and his blood pressure fell abruptly. Increasing the rate of administration of nikethamide produced no improvement. Artificial ventilation by positive pressure through a tracheostomy reduced the pCO₂ to 60-73 mm. Hg, but the hypotension persisted and he died. Necropsy was not performed.

Discussion

These observations show that nikethamide can overcome the respiratory depression in patients with acute ventilatory failure due to O₂ administration. They do not, however, suggest that this drug can be used with ease or confidence in routine practice. The quantities required are very large and the rate of administration is very critical. The effects of overdosage, although short-lived, are distressing and obviously put a considerable additional strain on already very ill patients. Unpublished observations by Dornhorst and Laurence (personal communication) are in agreement with these findings. The hypotension in the second patient may have been due to the drug. Less-detailed observations on two further patients have confirmed that the margin between the dose which stimulates the breathing and that which causes distress is narrow and difficult to judge. We nevertheless feel that the intermittent administration of nikethamide is of value, particularly to stimulate coughing, in patients with ventilatory failure due to chronic lung disease in whom O₂ is essential. The depressant effects of O₂ can be largely avoided by improved methods of O₂ administration (Campbell, in preparation).

Summary

The potential value of nikethamide, aminophylline, and sodium salicylate as respiratory stimulants has been investigated in patients with chronic lung disease and ventilatory failure. As a first step the effect of these drugs on the arterial CO₂ tension was measured with the patients breathing air.

Aminophylline (1 g. intravenously) had little or no effect in six patients.

Sodium salicylate (8 g. intravenously) produced significant and prolonged lowering of the pCO₂ in three patients. Reasons are given why further experience is desirable before using salicylate in routine practice.

Nikethamide (2.5 to 6.25 g. intravenously) produced significant but very transient reduction of the pCO₂ in

three patients with moderate and severe ventilatory failure but not in two patients with mild ventilatory failure.

Further observations are described showing that nikethamide can counteract the respiratory depression caused by O₂, but also showing the difficulties and dangers of trying to maintain ventilation by the continuous administration of this drug.

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RESECTION FOR PULMONARY TUBERCULOSIS*

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The bacteriological findings in tuberculous lesions resected from 100 consecutive patients, related to the type of chemotherapy given before operation, have already been described (Bottrill and Edge, 1957). The recovery of positive cultures, the incidence of bacterial resistance, and the surgical morbidity and mortality were very much greater in patients who had interrupted or inadequate chemotherapy than in those who had "satisfactory" chemotherapy, according to the regimes recommended by the Medical Research Council (1952, 1955).

The purpose of this paper, which describes the experience of these 100 and our next 70 consecutive patients whose resected specimens were examined bacteriologically, is to correlate the laboratory findings with the subsequent clinical course of the patients; and to assess the value of these findings in defining the place of resection in the management of pulmonary tuberculosis at the present time.

Clinical Material

This series of 170 consecutive patients has been followed up from fifteen months to four years after resection. They are divided into two groups according to the type of antibacterial treatment given. Group 1 (satisfactory chemotherapy) comprised 95 patients who had continuous treatment, in one course of at least six months before operation, in the following minimal

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