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VENTILATORY EFFECTS OF PRETHCAMIDE IN HEALTHY YOUNG MEN

BY

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The ventilatory effects of intravenous injections and infusions of prethcamide have been investigated with healthy young adult male volunteers. Ventilatory changes due to the drug were measured at constant inspired P_{CO_2} or constant alveolar P_{CO_2}, and in relation to the response to changes in alveolar P_{CO_2}. The experiments show that the drug is a mild and somewhat inconstant respiratory stimulant, slow and prolonged in action and liable to give rise to a variety of unpleasant side-effects.

Prethcamide (Micoren, Geigy) is a mixture of two di-alkyl amino fatty acids:

(1) $CH_3-CH_2-\underset{\displaystyle CH_3-CH_2-CH_2-N-CO-CH=CH-CH_3}{\overset{\displaystyle CH-CO-N(CH_3)_2}{|}}$

(2) $CH_3-CH_2-\underset{\displaystyle CH_3-CH_2-N-CO-CH=CH-CH_3}{\overset{\displaystyle CH-CO-N(CH_3)_2}{|}}$

Since Benstz (1953) demonstrated its analeptic properties, it has been widely accepted in France, Germany and Italy as a ventilatory stimulant in various types of respiratory failure. Thomas (1962), in the only British study so far reported, described moderate ventilatory stimulation by the drug in patients with various degrees of respiratory failure due to emphysema.

We have investigated the ventilatory effects of prethcamide in healthy young adult male volunteers. Side-effects and the prolonged action of the drug caused difficulties, but eleven experiments were technically satisfactory. They indicate that prethcamide is a relatively weak respiratory stimulant in tolerated doses.

METHODS

Gas mixtures containing 50% oxygen and various concentrations of CO_2 were supplied to the subjects, and ventilation, respiratory frequency and alveolar P_{CO_2} were measured, by methods previously described (Anderton, Cowie, Harris & Sleet, 1962; Anderton & Harris, 1963). During control periods isotonic saline, and during test periods prethcamide in isotonic saline, were given through an indwelling polyethylene catheter inserted into a superficial arm vein. The solution containing the drug was delivered from a constant-infusion pump. The

subjects were eleven healthy young men between 20 and 29 years old, whose weights ranged from 70 to 102 kg. They were studied in the afternoon, after fasting for 3 hr, in a semi-recumbent position on a comfortable bed, and were kept, as far as possible, ignorant of the procedure. During ventilatory measurements they were encouraged to read but were not allowed to fall asleep.

Experiments were of three kinds:

(1) In one subject the effect of single intravenous injections of prethcamide was compared with that of single saline injections; all injections were given via a two-way stopcock connected with the intravenous catheter.

(2) In five experiments lengthy infusions of prethcamide were given while ventilation was measured. In one of these alveolar P_{CO_2} was allowed to change with changing ventilation while inspired P_{CO_2} was kept constant, and in four alveolar P_{CO_2} was kept constant by increasing inspired P_{CO_2} as ventilation increased.

(3) The ventilatory response to CO_2 was studied with five subjects (a) using single injections of the drug (three subjects), and (b) using prolonged infusions (two subjects).

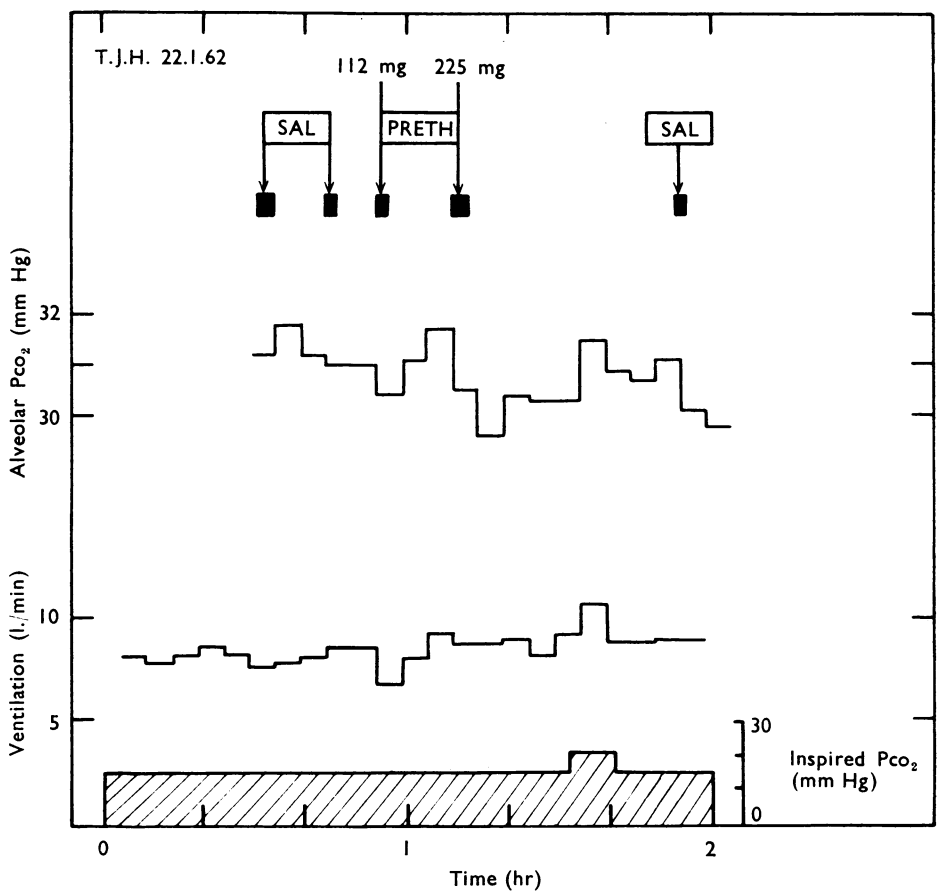

Fig. 1. The effect of single intravenous injections of isotonic saline (SAL) and of prethcamide (PRETH) on alveolar P_{CO_2} and ventilation. In this and subsequent figures 5-min mean values for ventilation rate and alveolar P_{CO_2} are shown. At 1 hr 32 min inspired P_{CO_2} was increased to bring alveolar P_{CO_2} back to the control level. No side-effects.

RESULTS

Single injections of prethcamide

Fig. 1 shows that the ventilatory effects of single injections of saline and of prethcamide cannot easily be distinguished. Ventilation was increased by only 0.5 l./min after 337 mg of the drug. However, alveolar P_{CO_2}, which is a more sensitive index than ventilation at low ventilation rates, fell about 0.5 mm Hg after 112 mg and about 1.0 mm Hg after a further 225 mg of prethcamide. Near the end of the experiment inspired P_{CO_2} was raised to bring alveolar P_{CO_2} back to the control level. This increased ventilation to 2 l./min above the control level. No side-effects were felt by the subject.

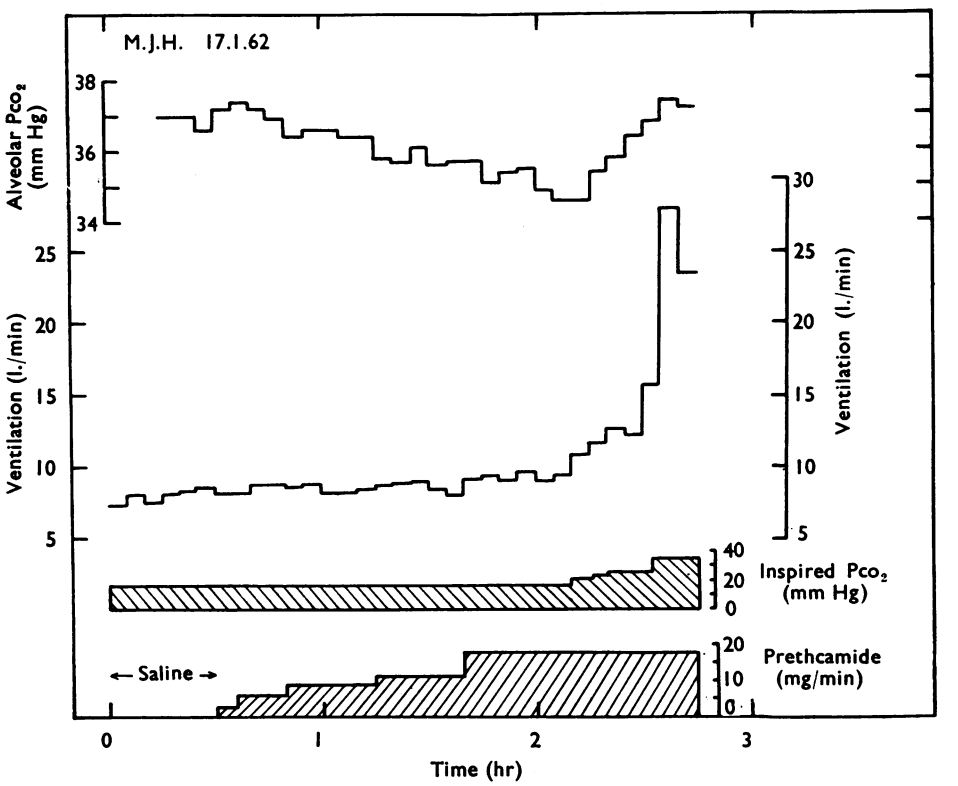

Fig. 2. The effect of infusion of prethcamide at five different rates on alveolar P_{CO_2} and ventilation. At 2 hr 10 min inspired P_{CO_2} was increased to bring alveolar P_{CO_2} back to the control level. No side-effects.

Infusions of prethcamide

Fig. 2 illustrates an experiment in which ventilation and alveolar P_{CO_2} were measured during the infusion of isotonic saline followed by prethcamide infusions at five different rates. Inspired P_{CO_2} was kept constant at 15 mm Hg until the end of the experiment, and the alveolar P_{CO_2} was thus free to fall with increasing ventilation. As the rate of infusion of prethcamide was increased in steps to a maximum

of 17.8 mg/min, the alveolar P_{CO_2} fell from 37 mm Hg to 34.6 mm Hg; at the 3rd and 4th infusion-rates the alveolar P_{CO_2} tended to attain a steady value. Ventilation rose very little and gradually. When alveolar P_{CO_2} was increased to the control level, the ventilation rate rose considerably; a steady state was not reached, but the mean values for alveolar P_{CO_2} and ventilation rate during the last 20 min were 36.95 mm Hg and 19.9 l./min respectively. The control ventilation at the same alveolar P_{CO_2} was 8.2 l./min.

For four subjects the inspired P_{CO_2} was adjusted throughout the infusion so that alveolar P_{CO_2} remained constant. The object was to determine a plan of dosage which would secure the rapid attainment of a steady state at the highest possible degree of stimulation without severe side-effects. Fig. 3 shows the results of giving

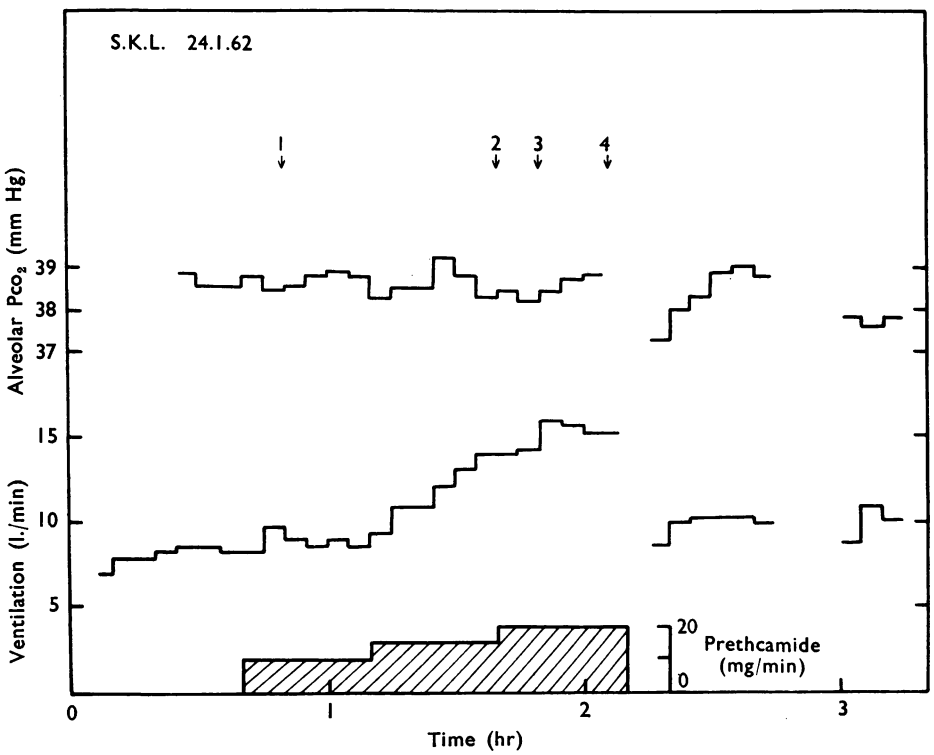

Fig. 3. Effect of prethcamide on ventilation at constant alveolar P_{CO_2}. Side-effects (at arrows): 1, Slight headache. 2, Desire to micturate, inability to do so. 3, Restlessness, tingling in legs. 4, Severe dizziness.

prethcamide at 10, 15 and 20 mg/min for 30 min at each rate. The control ventilation was 8.5 l./min. During the last 5 min of each of the first two infusion rates and the last 8 min of the 3rd, the ventilation rates were 8.6, 14.0 and 15.4 l./min respectively. The highest rate of infusion therefore gave little extra stimulation; however, it gave quite severe side-effects. Ventilation was still nearly 2 l./min higher than the control 1 hr after the infusion had been stopped. The rise in ventilation

during the infusion was gradual, and the side-effects were cumulative even after the rise in ventilation had stopped.

Three subjects were given " priming " doses of prethcamide followed by constant or declining infusions (Fig. 4). Subject J.M.O. showed a small rise in ventilation rate after each priming dose followed by a slow increase during a constant infusion at a low rate. Even after 3 hr, ventilation had not reached a definite steady state.

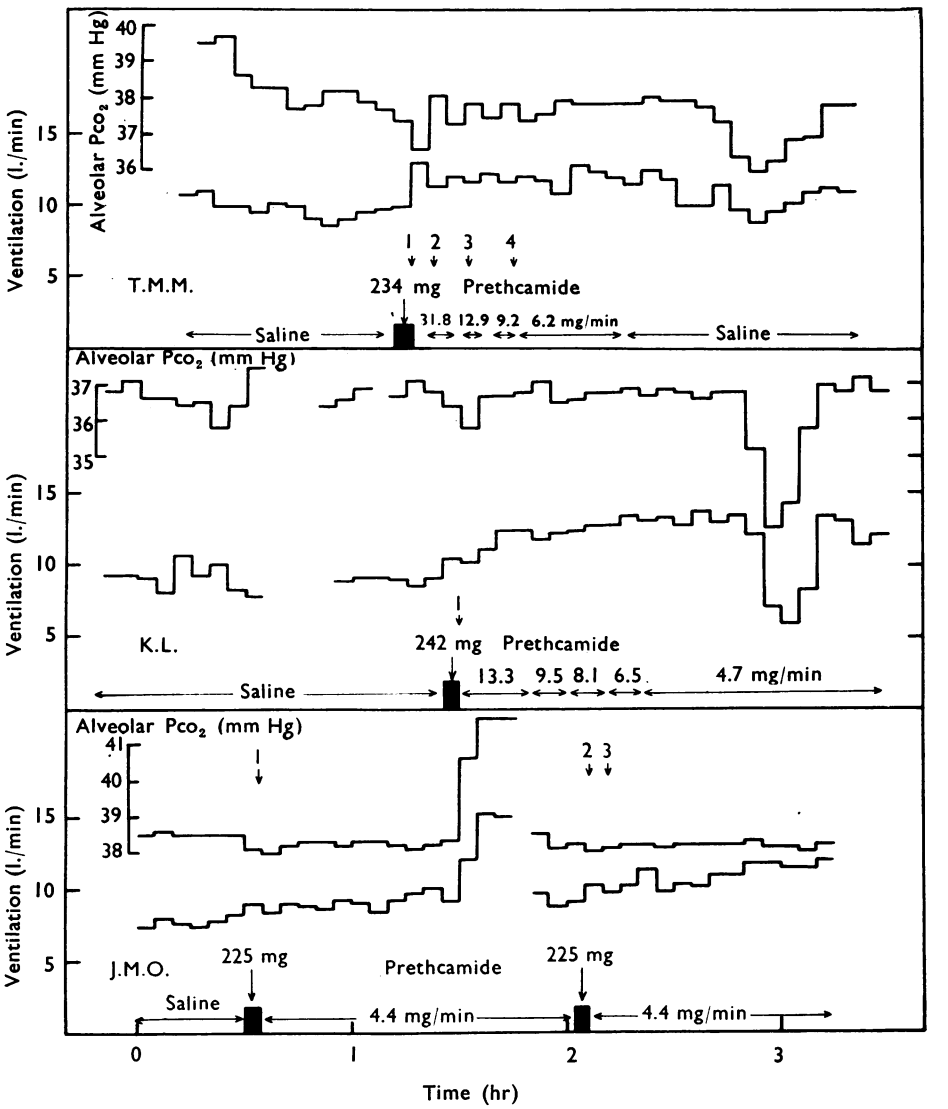

Fig. 4. Ventilatory responses to infusions of prethcamide at constant alveolar P_{CO_2} (3 subjects). Near the end of the experiment on K.L. inspired CO_2 was withdrawn, and on T.M.M. reduced to the original level, for a short time. Side-effects (arrows): T.M.M.: 1, Dizziness. 2, Tingling in feet. 3, Restlessness, tingling worse. 4, Tingling better but still present. K.L.: 1, Dizziness. J.M.O.: 1, Dizziness and flushing. 2, Dizziness. 3, Twitching in calves, tingling of legs.

The stimulation achieved was trivial; side-effects were limited to the 1 to 2 min following each priming dose. K.L. received no drug for the first 1.5 hr; there was some initial variation, but his record shows no definite trend in either direction until the drug is given. After the infusion had been started ventilation rose gradually from 9 l./min to a plateau at 13 l./min, and the increase was maintained until the infusion was stopped. Near the end of the experiment CO_2 was withdrawn from the inspired gas; ventilation fell to 6 l./min. In the experiment on T.M.M. a more rapid effect was obtained by giving a faster infusion at the beginning. Ventilation rose from 9 to 12 l./min and the increase was maintained, with side-effects, until the end of the infusion. Stimulation continued for 1 hr afterwards; a return, near the end of the experiment, to the original inspired P_{CO_2} resulted in a fall of 2 mm Hg below the control alveolar P_{CO_2}, indicating persistence of respiratory stimulation.

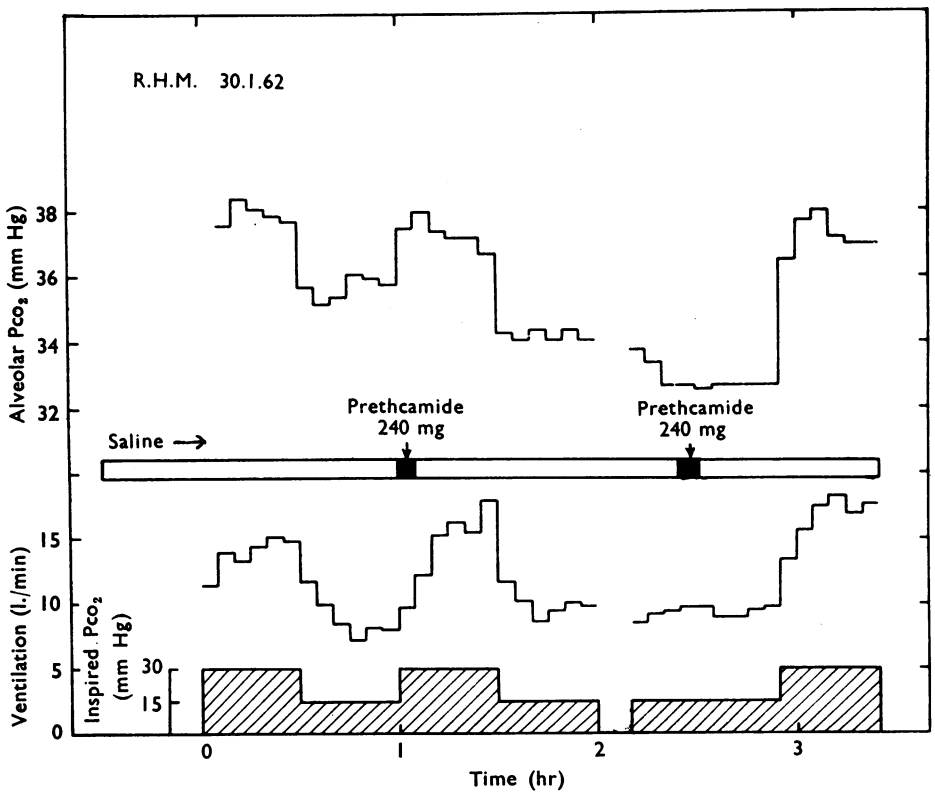

Fig. 5. Ventilatory response to CO_2 before and after single injections of prethcamide. Side-effects limited to dizziness at the end of each injection.

Response to CO_2 during the action of prethcamide

Single injections. Three experiments were carried out. Fig. 5 shows the results in one of these and the experimental design common to all three. Two steady states were studied, at inspired P_{CO_2}'s of 15 and 30 mm Hg respectively, before and after injections of prethcamide. Each injection was of 240 mg of the drug, given

over 5 min into the infusion tubing without the subject's knowledge. Because we were uncertain as to how long each injection exerted its effect, the order of the inspired CO_2 mixtures was reversed after the 2nd injection of prethcamide. Respiratory stimulation is shown by the greater ventilation and lower alveolar P_{CO_2} after the drug, for a given inspired P_{CO_2}. The three experiments are combined in Fig. 6 as a ventilation rate/alveolar P_{CO_2} plot; the procedure used to combine the data has been described elsewhere (Anderton *et al.*, 1962). In Fig. 6 points above

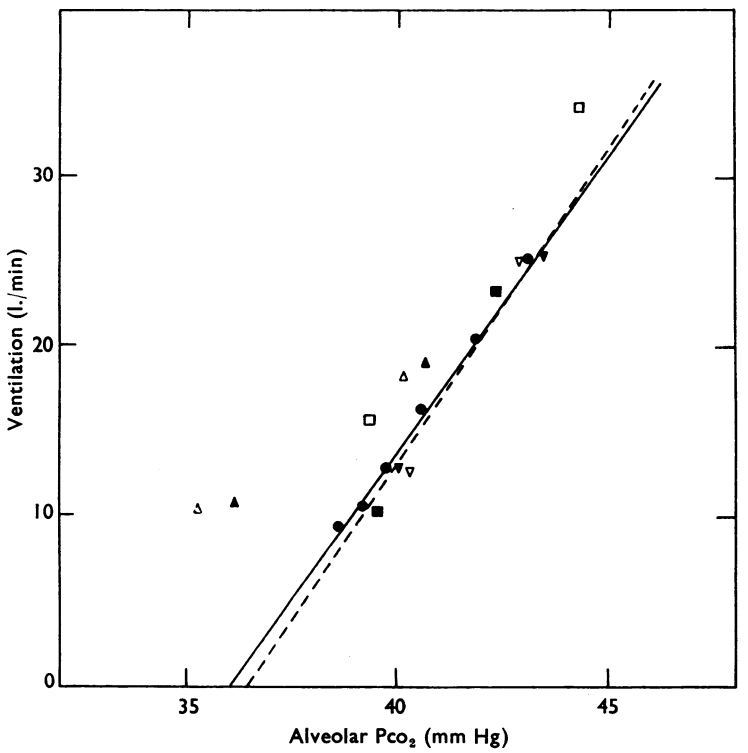

Fig. 6. Relationship of ventilation to alveolar P_{CO_2}; ● during infusion of saline; after 1st and 2nd injections of prethcamide, J.A.A.H. ■ and □, R.H.M. ▲ and △, M.M.K. ▼ and ▽. The data have been adjusted so that the saline points all lie on the same straight line with an intercept of 36 mm Hg and a slope of 3.5 l./min/mm Hg. The dotted line shows the expected result of repeating the observations without injecting any drug (six subjects).

the control line represent stimulation, points below depression of breathing. Four points lie just below the line; of these three are from subject M.M.K., who was more than 20 kg heavier than the other two subjects. The remaining eight points lie above the control line, and except for the highest point they lie further from it at low levels of alveolar P_{CO_2} than at high levels.

Infusions. Subject C.C. was studied during a control period on saline infusion and during infusion of prethcamide, the rates of which were based, weight for weight, on those which had given a fairly rapid attainment of a ventilatory plateau with

subject T.M.M. The method to determine ventilatory response to CO_2 was the two-way unsteady-state " loop " technique described by Anderton & Harris (1963). This method is rapid and is believed to give an accurate estimate of the steady-state relationship between the two variables. The result is shown in Fig. 7. No respiratory stimulation by the drug is shown.

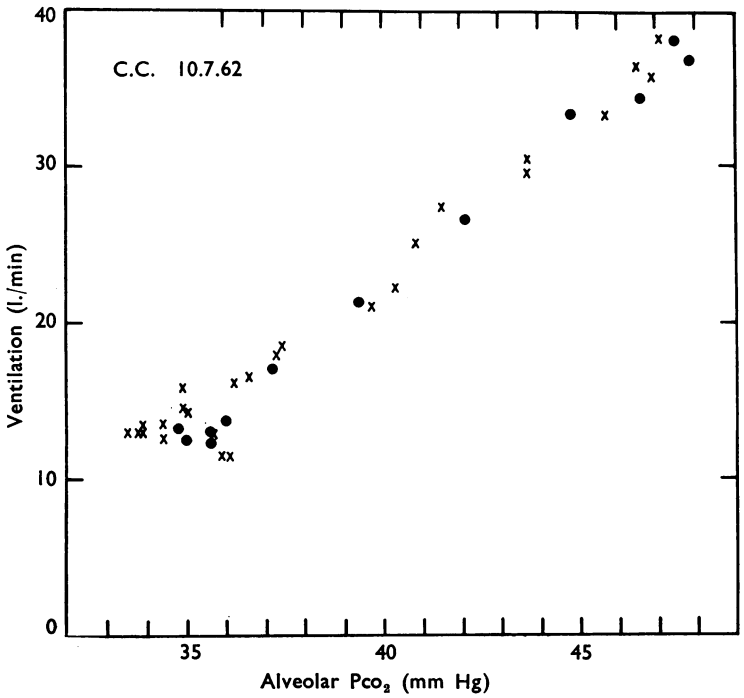

Fig. 7. Ventilatory response to CO_2 in subject C.C., ● during saline infusion, x during prethcamide infusion. Each point represents mean values of ventilation rate and alveolar P_{CO_2} during successive 2-min periods of a 2-way changing state corrected for time-lag between change in alveolar P_{CO_2} and response of ventilation (Anderton & Harris, 1963).

K.S.S. was given an infusion at a constant rate of 15 mg/min. Inspired P_{CO_2} was varied during the control and test periods to obtain two steady states in each period. When plotted from the data of Fig. 8, the ventilation rate/alveolar P_{CO_2} line is not altered by the drug. Side-effects began 18 min after starting the infusion and increased in severity and variety as it continued.

Side-effects

These were numerous and varied, and their nature and order of appearance are detailed in the legends to Figs. 3, 4 and 8. They were severe in one subject, moderate in four, mild in four and absent in two. In the four cases classified as mild the side-effects occurred only towards the end of a single injection or priming dose, and passed off rapidly. The more severe symptoms occurred during prolonged infusions of the drug, but there was no close relationship between the rate or duration of the

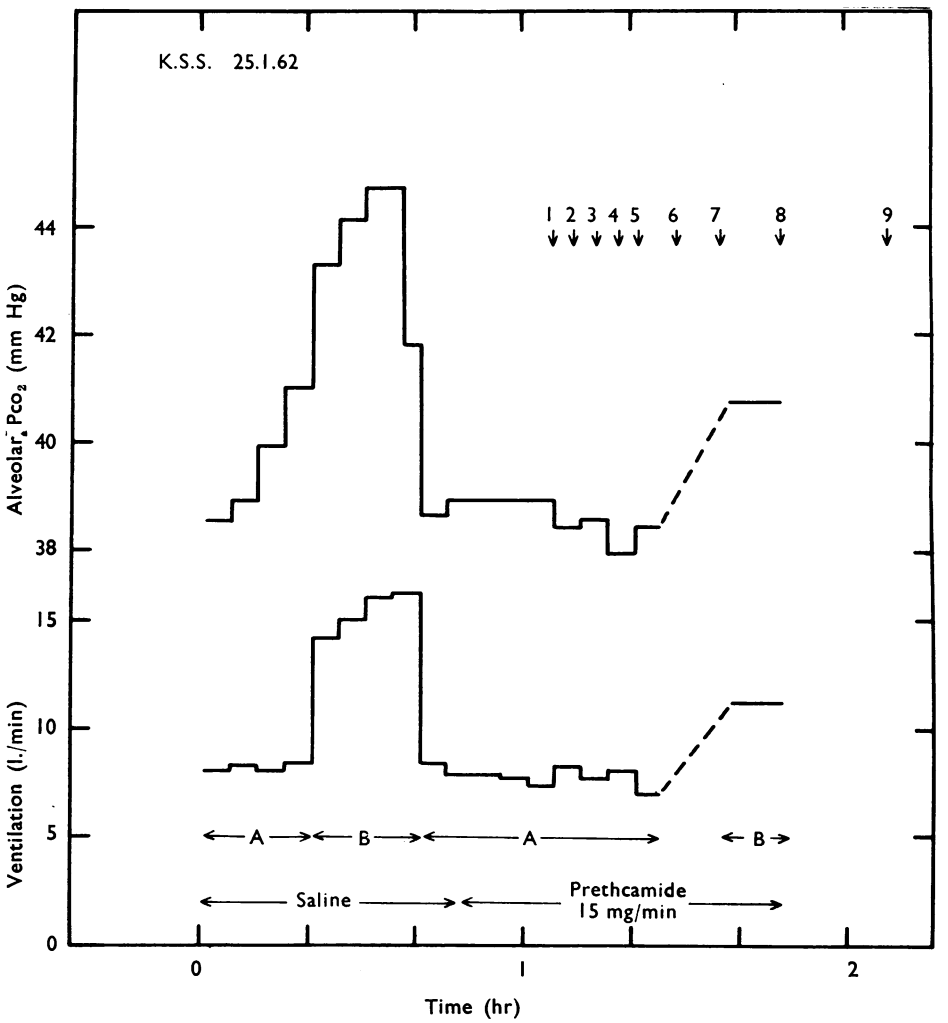

Fig. 8. Ventilatory response to CO_2 in subject K.S.S. during infusions of saline and prethcamide. A and B represent periods of low and high inspired P_{CO_2} respectively. Side-effects (arrows): 1, Dizziness. 2, Difficulty in near vision. 3, Tingling of legs, starting in feet and gradually involving whole of both legs. 4, Sensation of distended bladder. 5, Sweating. 6, Failure of prolonged attempt at micturition. 7, Incoordination on getting back on the bed. 8, Intense desire to micturate but still unable to do so. 9, Dizziness and blurred vision still present but desire to micturate passing off.

infusion and the appearance of side-effects. Like the increase in ventilation, side-effects might persist up to 1 hr after stopping an infusion.

DISCUSSION

In conscious subjects an increase of ventilation may accompany any unpleasant sensation and therefore a drug need not be a specific respiratory stimulant to increase

ventilation. These experiments show, however, that prethcamide can stimulate breathing in the absence of side-effects and it is, therefore, a true respiratory stimulant. The greatest stimulation, indeed, was obtained in a subject who experienced no side-effects (Fig. 2).

In relation to dose, the stimulation of breathing was variable. The increase in ventilation appeared to be related to the total quantity of drug infused rather than to the rate of infusion at any particular moment; this is what one would expect of a drug with a prolonged action. Fig. 9 shows that, in general, stimulation increases

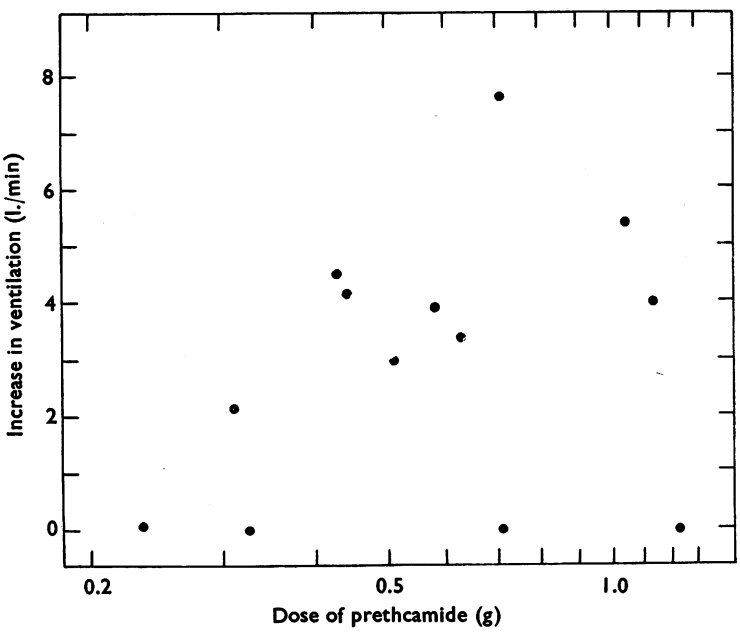

Fig. 9. Increase in ventilation rate above control value in relation to the dose of prethcamide given. The data were somewhat arbitrarily selected from the experimental results, but in general denote the state of affairs at the end of an infusion if no steady state was reached, the beginning of a steady state if this was reached, or the highest ventilation rate after a single injection of the drug. Comparisons between saline and drug periods were made at the same alveolar P_{CO_2}'s in each case. Both the dose of prethcamide and the change in ventilation have been corrected to a standard body-weight of 65 kg.

with the total dose but suggests that no effect can be expected in an adult after a dose smaller than 200 mg. Apart from one point (increase in ventilation = 7.6 l./min) it appears that little advantage is to be gained by giving more than 450 mg, at least over the course of an hour or two. Three subjects failed to show an increase in ventilation after doses up to 1.2 g.

While the prolonged action of prethcamide might have some therapeutic advantages, the delay in reaching a steady state and the occurrence of delayed and cumulative side-effects during constant infusion make the drug more difficult to investigate than one with a shorter action. For this reason some initial conventional

experiments on the response to CO_2 had to be abandoned, and we were obliged to devise other ways of obtaining the information required. The administration of two single doses of drug, followed by low and high CO_2 mixtures in reversed order (Fig. 5), is one way in which this can be done, although it yields only two points each in duplicate and the shape of the CO_2/response line cannot be determined. The unsteady-state method (Fig. 7) gives more points and takes less time than the conventional steady-state method, and is well suited to studies of the action of drugs which may alter the shape of the normally straight CO_2/response line ; in the instance shown in Fig. 7 the drug produced no ventilatory effect. Fig. 6, based on single injections, suggests that the stimulation of breathing by prethcamide is more marked at low values of alveolar P_{CO_2}. In this respect the drug is similar to ethamivan (Anderton *et al.*, 1962). In our studies of ethamivan we suggested that at low alveolar P_{CO_2} ventilation was independent of CO_2 during the action of the drug, but we have not yet investigated this point in detail. So far as prethcamide is concerned, this is not so ; thus Fig. 4 (K.L.) shows that a marked fall in ventilation rate occurred when CO_2 was withdrawn from the inspired gas: if independence of CO_2 does occur with prethcamide, it must operate only within certain limits.

Prethcamide is capable of about the same degree of respiratory stimulation as ethamivan, but seems to be less constant in its effect ; some subjects do not respond at all, although they may experience side-effects. Prethcamide acts less quickly than ethamivan when given by infusion and a steady state of stimulation is longer deferred. Side-effects are more frequent, more unpleasant and less easily anticipated, and they take much longer to disappear when the infusion is stopped. On the other hand, an increase in ventilation persists longer after administration of prethcamide, and single intravenous injections (which do not carry the same risk of cumulative side-effects) are probably as efficient as continuous infusions.

The doses of prethcamide in these experiments are of the order recommended for clinical use. The ventilatory responses were mostly too small to be decisive in the clinical situations which call for the use of a respiratory stimulant, unless the relative increase in ventilation due to the drug is greater in disease than in health. This may sometimes be so, although there is little firm evidence of it (Hahn, 1960).

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