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THE EFFECTS OF NOSCAPINE AND CODEINE ON THE VENTILATORY RESPONSES TO EXCESS OF CARBON DIOXIDE AND LACK OF OXYGEN

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The pharmacological effects of noscapine were first thoroughly studied by Chopra, Mukherjee & Dikshit (1930). They concluded that this opium alkaloid relaxed the smooth muscle of the uterus, gall bladder, urinary bladder, bronchi and arterioles by a direct action, potentiated the analgesic effects of morphine and increased the rate and amplitude of respiratory movements by a central action. The action of noscapine in suppressing cough has been described by Winter & Flataker (1954), Konzett (1955), Bickerman, German, Cohen & Itkin (1957), La Barre & Plisnier (1959) and others. Its freedom from serious toxic effects in doses up to 100-times the antitussive dose (Winter & Flataker, 1961; Lasagne, Owens, Shnider & Gold, 1961) and its lack of habit-forming properties (World Health Organization, 1959) suggest its clinical use as a cough-suppressant.

The earlier reports of a stimulant action on the respiratory centre were reinvestigated by Belville, Wallenstein, Wald, Dowling & Houde (1958), who found no evidence of either stimulation or depression of the ventilatory response to carbon dioxide in man. Hypoxic responses were not investigated. There is evidence that a drug may affect responses to hypoxia and carbon dioxide independently (Harris & Slawson, 1965) and the clinical use of a cough-suppressant often involves the treatment of patients who are hypoxic. The effects of noscapine and codeine on the ventilatory responses to both carbon dioxide and hypoxia have therefore been compared.

METHODS

The subjects were all healthy young adult volunteers, either medical students or nurses. Experiments were done in the afternoon, with the subjects semirecumbent on a comfortable bed after having fasted for 2.5 hr. Each subject was told that the purpose of the study was to determine the effect of a harmless drug on the breathing but the drugs were not specified until after a given subject's last attendance. During all experiments the subjects were required to concentrate on reading a book.

Inspired gas mixtures were supplied, ventilation ($\dot{V}$) was measured and alveolar gas collected by methods previously described (Cunningham, Cormack, O'Riordan, Jukes & Lloyd, 1957; Anderton & Harris,

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1963). Five different inspired gas mixtures were supplied in turn, before and after administration of the drug. The order of administration of these mixtures, their composition and duration of administration were as follows:

Mixtures	P_{O_2} (mm Hg)	P_{CO_2} (mm Hg)	Duration (min)
1 and 6	250	20	14
2 and 7	250	35 or 40	19
3 and 8	100	30 or 35	11
4 and 9	80	30 or 35	9
5 and 10	70	30 or 35	9
		Total	62

During the last 4 min of each administration of a mixture a sample of alveolar gas was collected. The timing of samples during the low oxygen mixtures was primarily decided by the attainment of a steady state of alveolar P_{O_2} which was monitored by means of a paramagnetic analyser. Mixtures 1, 2, 6 and 7 were analysed for carbon dioxide, and the rest for both carbon dioxide and oxygen, in the Haldane apparatus.

Immediately after the fifth mixture an oral dose of either noscapine or codeine was given. The doses given to each subject are shown in Table 1. The drugs were made up in tablets of identical appearance

TABLE 1

DRUGS AND DOSES GIVEN TO EACH SUBJECT
An asterisk means that the indicated drug and dose was given

Subject	Sex	Noscapine		Codeine	
		50 mg	100 mg	30 mg	60 mg
I.A.	M	*	*		
N.C.	F	*	*	*	
C.McL.	F	*	*		*
J.A.R.S.	M	*		*	
J.G.	M	*			
E.Sp.	F		*	*	*
J.K.	F		*		
E.S.	F			*	
J.C.	M				*
P.T.	F			*	
Totals		5	5	5	3

containing either 25 mg of noscapine or 15 mg of codeine, as alkaloid. The flavouring agent was the same but did not fully disguise a difference in taste between the two drugs. After chewing and swallowing the tablets, each subject rested for 30 min, emptied the bladder, rested for a further 10 to 15 min and then started breathing mixture 6.

Calculations. Measurements of $\dot{V}$ and P_{A,CO_2} on mixtures 1, 2, 6 and 7 provided the values for the $\dot{V}/P_{A,CO_2}$ lines before and after the drug in the virtual absence of the hypoxic stimulus. Mixtures 3, 4, 5, 8, 9 and 10 each gave a $\dot{V}/P_{A,CO_2}$ point at a known, low P_{A,O_2}, the first three before and the last three after the drug. All values were standardized and hypoxic responses were calculated as previously described (Anderton, Harris & Slawson, 1964; Harris & Slawson, 1965). The control studies of Anderton *et al.* (1964) were used to assess the effects of the drugs. The significance of differences between means was assessed by means of the *t*-test.

RESULTS

Response to carbon dioxide. The responses to carbon dioxide in the virtual absence of the hypoxic stimulus are shown in Figs. 1 and 2 as scatter diagrams of $\dot{V}/P_{A,CO_2}$ points

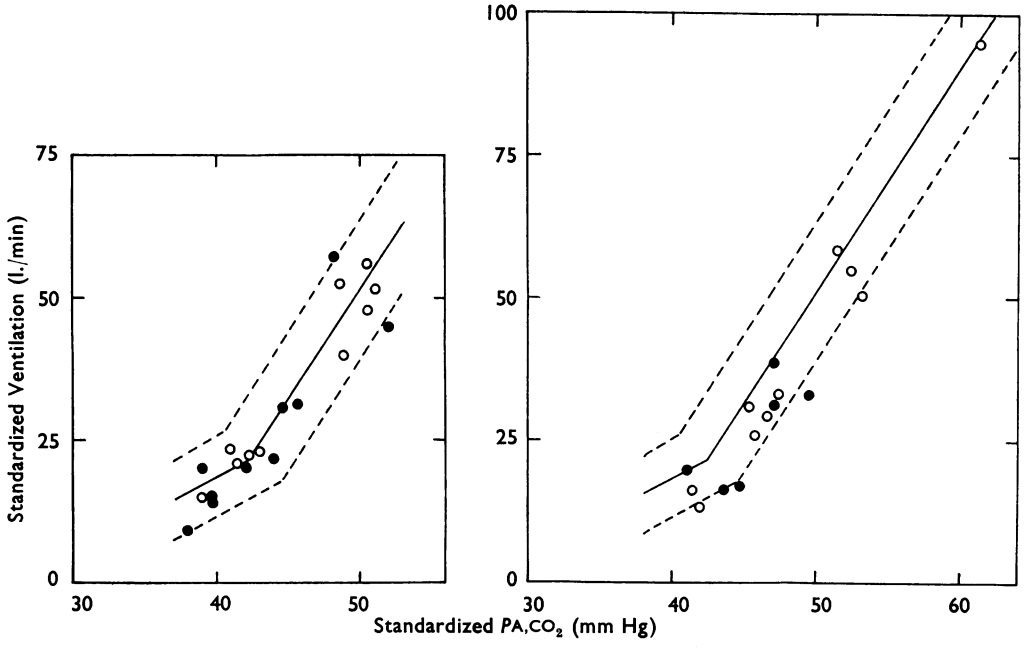

Fig. 1. Ventilatory response to carbon dioxide after noscapine; ○ 50 mg, ● 100 mg. Lines indicate regression ± two standard deviations of ventilation for the second period of repeatability studies (for calculation see Harris & Slawson, 1965).

Fig. 2. Ventilatory response to carbon dioxide after codeine; ○ 30 mg, ● 60 mg. Lines as in Fig. 1.

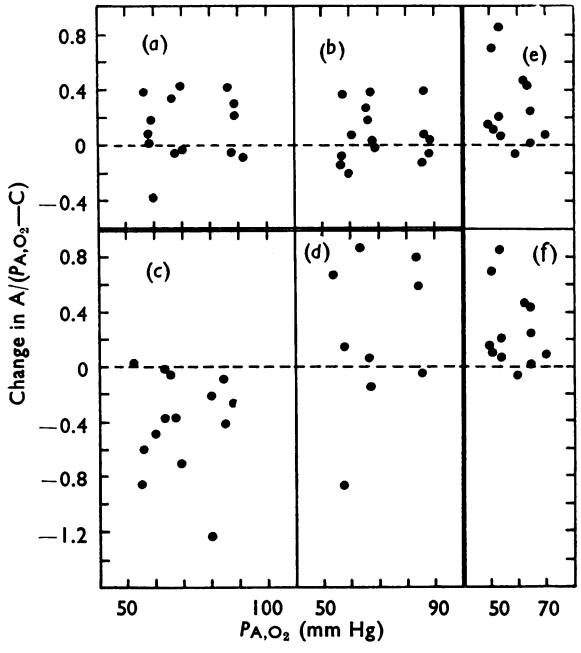

Fig. 3. Change in ventilatory response to hypoxia after (*a*) 50 mg of noscapine, (*b*) 100 mg of noscapine, (*c*) 30 mg of codeine, (*d*) 60 mg of codeine; (*e*) and (*f*), no drug, for comparison. The hypoxic response is expressed as $A/(P_{A,O_2}-C)$ (Lloyd, Jukes & Cunningham, 1958).

during the periods after the drug. In each figure these points can be compared with the regression lines and 95% tolerance limits calculated from forty-four observations made during experiments in which no drug was given (Anderton *et al.*, 1964). The results from the experiments in which noscapine was given (Fig. 1) obviously fall evenly over the expected range and there is no difference in this respect between the two doses given. The $\dot{V}/P_{A,CO_2}$ points from the experiments in which codeine was given (Fig. 2) nearly all fall in the lower half of the expected range. The mean deviation of these points from the control regression is not significant for either dose given.

Response to hypoxia. Fig. 3 shows the changes in response to hypoxia after noscapine and codeine respectively, compared with the expected change when no drug was given. It is clear that 50 or 100 mg of noscapine had little or no effect (for 50 mg, $0.20>P>0.10$; for 100 mg, $P=0.05$). After 30 mg of codeine, however, the hypoxic response was markedly depressed ($P<0.001$). Increasing the dose of codeine to 60 mg resulted in a normal response to hypoxia ($P>0.90$), although the scatter of results is greater than in the control group and at least two points suggest depression of the response.

DISCUSSION

The actions of noscapine and codeine on the ventilatory response to carbon dioxide without hypoxia, observed in this study, are similar to those reported by Belville *et al.* (1958). These authors compared the response to carbon dioxide after drug administration with that before the drug was given. They found that noscapine had no effect whereas codeine depressed the response. The present study, in which responses after the drug were compared with a standard based on repeatability measurements, confirms their finding with respect to noscapine. After codeine, $\dot{V}/P_{A,CO_2}$ points nearly all indicate depression compared with the regression line for the repeatability studies (Fig. 2), and the degree of this depression is similar to that reported by Belville *et al.* (1958). Nevertheless, when the standard deviation of repeatability values about regression is taken into account, the depression after codeine does not reach the 5% level of significance. This, of course, does not prove that there is no depression but suggests that the observed results could have been due to a sampling effect. At most, depression could only have been slight. There appears to have been no difference in this respect between the two doses of codeine given.

The present experiments also indicate that noscapine, in the doses given, has no measurable effect on the ventilatory response to hypoxia (Fig. 3,*a* and *b*). In contrast, 30 mg of codeine produced a striking depression of the hypoxic response; all but one of the points in Fig. 3,*c* lie below the line of zero change in hypoxic response, whereas all but one of the control points lie above it. The larger dose of codeine (Fig. 3,*d*), however, did not accentuate the depression seen with 30 mg, but on the contrary produced a normal response. It may be that with 60 mg of codeine two mechanisms are involved—a primary depression of the hypoxic response, seen alone after a dose of 30 mg, complicated by the excitatory effect which codeine shares with morphine. In support of this view, it may be noted that two of the three subjects given 60 mg of codeine complained spontaneously of unease and apprehension during the period after the drug, whereas the five subjects given 30 mg were not aware of these or indeed any effects. The same explanation might apply to the failure of this study to show a difference in response to carbon dioxide between the doses of codeine, referred to above.

This investigation was not concerned with the relative merits of noscapine and codeine as cough suppressants; this question has been dealt with in several publications already mentioned. According to these, 50 mg of noscapine is at least as effective as 30 mg of codeine as a cough suppressant. Both drugs show their full antitussive effect 1 hr after ingestion and this is maintained for at least 2 hr. The ventilatory measurements made in the present study therefore coincided with the full antitussive action of the drugs. The results suggest that from the standpoint of respiratory depression noscapine is safe and in this respect is to be preferred to codeine in therapeutic use.

The conclusion that 30 mg of codeine depresses the hypoxic response more than the response to carbon dioxide is of interest. The common conception of the hypoxic stimulus as a " rugged " one, less influenced by drugs than the response to carbon dioxide, receives no support from this finding. It has already been suggested that cyclobarbitone may depress the hypoxic response while leaving the response to carbon dioxide unaffected (Harris & Slawson, 1965). It is evident that more attention must be given to the hypoxic stimulus when the action of drugs is being investigated.

SUMMARY

1. The ventilatory responses to excess of carbon dioxide and lack of oxygen were studied before and after noscapine (50 and 100 mg) and codeine (30 and 60 mg).

2. Neither dose of noscapine had a demonstrable effect on the response to either carbon dioxide or hypoxia.

3. Both doses of codeine slightly depressed the response to carbon dioxide, but the effect was statistically insignificant compared with controls; 30 mg of codeine, but not 60 mg, caused a highly significant reduction in the response to hypoxia and provided new evidence that a drug may selectively depress the hypoxic response without affecting the response to carbon dioxide.

4. In respect of respiratory depression, noscapine is a safe cough suppressant and is preferable to codeine.

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