EFFECT OF NOSCAPINE AND CODEINE ON THE RESPIRATORY RESPONSE TO CARBON DIOXIDE

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Noscapine (formerly called narcotine) is a benzylisoquinoline type compound which is related to papaverine. Although it makes up 6 per cent of the alkaloid content of opium, it does not have the properties associated with narcotics of the phenanthrene type. Noscapine has been shown to be an effective antitussive in animals (1, 2). Evaluation of its antitussive action on experimentally produced cough in human beings has shown 5 mg. of noscapine to be more effective than 30 mg. of codeine (3). Ten to 60 mg. of noscapine has been used clinically to treat cough in patients with pulmonary emphysema. In 70 patients studied, relief comparable to that attained with equivalent doses of codeine was obtained (4). The respiratory effects of this drug in human beings have not been completely studied. Therefore, this study was designed to evaluate the respiratory effects of noscapine in man in terms of the alveolar ventilation—alveolar P_{CO_2} curve and to compare them with the respiratory effects of another antitussive, codeine.

METHOD

The equipment used in this study is schematically shown in figure 1. Both the basic method and the equipment are the same as those used by Seed, Wallenstein, Houde, and Bellville (5), and Steinberg, Bellville and Seed (6), and represented a modification of the technique described by Eckenhoff, Helrich and Hege (7). Each subject is fitted with a rubber nose clip and a rubber mouth piece. The expiratory gases of the subject pass through a J-2 Warren Collins one-way flutter valve, to a Liston-Becker Model 16 infrared carbon dioxide gas analyzer. The volume of the expired gas is measured by a Hospital Gas Meter (American Meter Co.), and the temperature of the gas is measured by a thermometer placed at the entrance to the gas meter. A photo cell is attached to the gas meter dial so that a blip for every 500 cc. of gas is recorded on one channel of a two-channel Sanborn recorder. On the other channel, a continuous recording of carbon dioxide concentration in the exhaled air is made. By using two 3-way valves and a flexible oxygen reservoir, the patient can breathe room air. With

both valves closed and 6 liters of oxygen in the reservoir, the subject can rebreathe in a circle system. In the circle system, the subject rebreathes his own expired gases, thus building up a measurable concentration of carbon dioxide in the system. The rebreathing procedure or "run" usually lasted seven minutes at the end of which time the P_{CO_2} approached 60 mm. of mercury. The normal alveolar carbon dioxide was measured by giving the command, "All the way!", as expiration started, whereupon the subject would exhale forcibly, and the end alveolar carbon dioxide sample would be trapped in the system. When the subject had been rebreathing for at least two minutes in a closed system, this was found to be unnecessary, since at high tidal volumes the end expiratory carbon dioxide sample closely approaches the alveolar carbon dioxide value. Oxygen concentration in the system was measured by an A. O. Beckman Model D oxygen analyzer at the
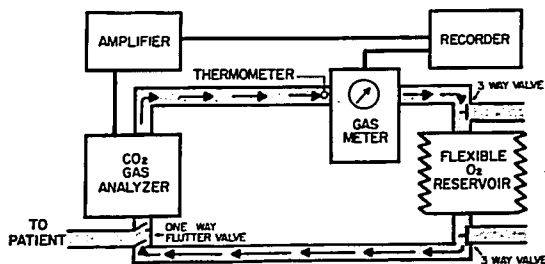

FIG. 1. Schematic diagram of equipment used to study effect of noscapine and codeine on the respiratory response to carbon dioxide. (By permission of The Willinms & Wilkins Company from J. Pharmacol. & Exper. Therap. 121: 71, 1957.)

beginning and the end of each run. The oxygen content in the closed system was always between 30 and 40 per cent.

To evaluate the respiratory effects of noscapine and codeine, a double-blind study was set up. Five healthy, conscious subjects were used for the experiment. Four coded bottles containing identically appearing capsules were prepared so that the experimental dose in each bottle was contained in one capsule. The drugs were administered in a random order; no two drugs were given within any thirty-six hour period. The investigators did not know the code until all the observations had been completed. The drugs and dosages employed were (1) noscapine, 30 mg.,* (2) noscapine, 90 mg., (3) codeine, 60 mg.,† and (4) lactose placebo.

Two control runs were recorded prior to each unknown. Following the second control run, the subject ingested one of the capsules containing the unknown. A run was then taken at one hour, and a second run at two hours post ingestion. Each subject had two control runs and two test runs for each unknown. The instrument was calibrated before and after each run with carbon dioxide-oxygen mixtures delivered from separate cylinders whose contents had been assayed by the micro-Scholander ‡ method. If there was a drift in P_{CO_2} of more than 1 mm. of mercury in the calibration curve, the run was redone. The barometric pressure was recorded following the last run and all gas volumes were corrected to body temperature and standard pressure. The dead space for each subject plus the valve and the mouth piece
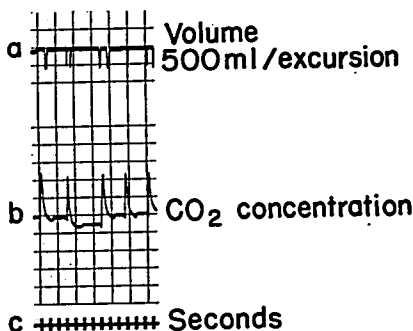

FIG. 2. Detail of typical record. (A complete typical record has been published, J. Pharmacol. & Exper. Therap. 121: 73, 1957.) Each "blip" on the top line (a) represents 500 cc. of expired air. The middle tracing (b) represents the carbon dioxide concentration of the exhaled gas. The gas initially exhaled from the upper respiratory passages has a low carbon dioxide content which increases with exhalation until the end alveolar P_{CO_2} is reached. The third line (c) represents the time base in seconds.

was assumed to be 180 cc. per breath and was used to correct minute volume to alveolar ventilation. A portion of a typical run is shown in figure 2.

For each unknown given to each subject, a graph was plotted of alveolar ventilation versus alveolar P_{CO_2} (fig. 3) for both control periods and for one and two hours after drugs. The alveolar ventilation is the ordinate, and alveolar P_{CO_2}, the abscissa. From these graphs, the displacement in terms of P_{CO_2} at an alveolar ventilation of 15 liters per minute was determined for each unknown at one and two hours, assuming a common mean slope which was arrived at

‡ We wish to thank Miss Margaret E. Hood for performing these determinations.
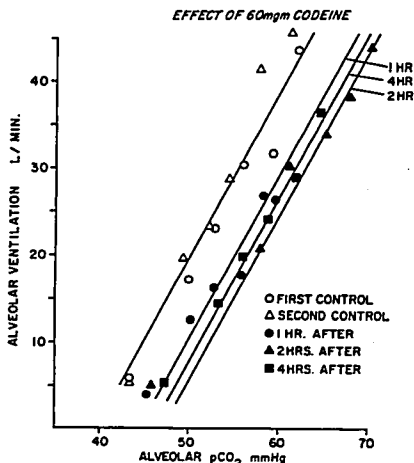
FIG. 3. The response curve for subject 4, before, 1, 2, and 4 hours after 60 mg. codeine.

for each subject from the composite of all the control data for each subject.

RESULTS

Respiratory depression was assessed as the displacement of the postmedication curves from the control curves. This displacement was expressed in mm. of mercury P_{CO_2}. The displacement at one and two hours after drug were tabulated with 4 entries for treatment and 5 for subject (table 1). The two-hour values were used in the calcula-

TABLE 1

DISPLACEMENT OF RESPONSE CURVE IN MM. OF MERCURY P_{CO_2}

Subject Number	Placebo		Noscapine (30 mg.)		Noscapine (90 mg.)		Codeine (60 mg.)	
	1 Hour	2 Hour	1 Hour	2 Hour	1 Hour	2 Hour	1 Hour	2 Hour
1	1.5	−0.8	0.3	1.7	1.5	−1.0	0	0
2	0	1.3	− .5	1.6	1.3	0	2.2	4.6
3	− .5	1.7	0.7	−3.3	− .8	−3.4	0	1.1
4	1.4	0	1.0	−2.8	1.1	1.7	5.0	6.4
5	−1.5	0.5	−2.2	0.7	1.3	−1.0	4.0	4.5
Mean	.18	.54	− .14	− .42	.88	− .74	2.24	3.32

TABLE 2

ANALYSIS OF VARIANCE

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Ratio
Total	19	121.06		
Patient	4	21.30	5.32	1.31
Treatment	3	51.08	17.03	4.19*
P × T	12	48.68	4.06	

* F for $P_{0.05} = 3.49$.

tion.   Positive values indicate respiratory depression, that is, a shift of the curve to the right; negative values indicate respiratory stimulation.

An analysis of variance of the two-hour data was then made (8), (table 2).   The variance due to treatment is significant beyond the 5

TABLE 3

ORTHOGONAL COMPARISONS

Totals (2 hours)	Placebo 2.7	Noscapine (30 mg.) 2.1	Noscapine (90 mg.) 3.7	Codeine (60 mg.) 16.6	F Ratio
	—	—	—	3+	11.49*
		+	—		0.06
	2+	—	—	.	1.03

* F for $P_{0.01} = 9.93$.

per cent level of F, while the variance due to subject is not significant. By orthogonal comparisons (8) (table 3), the respiratory effects caused by codeine were found to be highly significant ($P > 0.01$).   There was no significant difference between the effects of 30 mg. and 90 mg. of noscapine nor between the effects of lactose and noscapine.

DISCUSSION

Assay of respiratory depression by measuring minute volume before and after drug may not assess true respiratory effects, but rather a combination of respiratory and metabolic effects.   The product of alveolar ventilation and alveolar P_{CO_2} equals the carbon dioxide excretion.   If there is a decrease in carbon dioxide production, there will be a decrease in ventilation.   Therefore, a decrease in ventilation thought to represent respiratory depression would actually be due to a decreased rate of metabolism.   In the present study we define respiratory effects in terms of changes in the response curve so that these metabolic effects will not be misinterpreted as respiratory effects.   A complete critique of the methods used to study respiratory depression

may be found in the paper of Seed, Wallenstein, Houde, and Bellville (5).

Macht (9) demonstrated that noscapine caused dilation of the bronchi. This would mean that there would be an increase in respiratory dead space following the administration of noscapine and that the true alveolar ventilation would be lower than that calculated assuming no change in dead space. Failure to allow for an increase in dead space would displace the alveolar ventilation-P_{CO_2} response curve to the right, or in this study, in the direction of respiratory depression. There are no adequate data for change in dead space following drug. Therefore, it is impossible to correct for this variable. However, a 30 per cent increase in dead space produces a shift in the response curve of only 0.4 mm. of mercury P_{CO_2} to the right (5), so that if the change in dead space was of this magnitude and this factor was included in the calculations, the displacement of the curves to the left following noscapine would be less than calculated. The over-all effect would be for the noscapine data more closely to approximate that for placebo.

We employed the displacement of the alveolar ventilation-P_{CO_2} curve at two hours as the basis for comparing the effects of noscapine and codeine. The analysis was calculated using the one hour data and the conclusions were the same. It is interesting to note that the peak respiratory depression caused by codeine varied from subject to subject. Subject 3, who had a depression two hours following codeine of 1.1 mm. of mercury P_{CO_2}, at 4 hours following codeine had a depression of 3.4 mm. of mercury P_{CO_2} and subject 1, who showed no effect with codeine at 2 hours, experienced maximal subjective effects at four hours. However, in subject 4 the depression at four hours was less than at two hours after codeine (fig. 3). If frequent runs had been made so that maximal effects could be used in the calculations the difference between noscapine and codeine would probably be more striking.

Five to 60 mg. of noscapine has been shown to be an effective antitussive for treating cough induced by irritative or allergic phenomena in man (3, 4). Our results indicate that noscapine in doses up to 90 mg. in man does not produce significant respiratory stimulation or depression.

SUMMARY

A double blind study was carried out to evaluate the respiratory effects of noscapine and codeine. Displacement of the alveolar ventilation-alveolar P_{CO_2} curves was analyzed statistically. The results show that 60 mg. of codeine orally is a respiratory depressant, and that 30 mg. and 90 mg. of noscapine orally has no significant respiratory effect.

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