THE EFFECT OF DIHYDROCODEINE UPON RESPIRATION AND CIRCULATION IN MAN

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IN A RECENT publication, Gravenstein, Smith, Sphire, Isaacs, and Beecher (5) have expressed the opinion that 30 mg. of dihydrocodeine had almost the same analgesic potency as 10 mg. of morphine. They also believed that dihydrocodeine was essentially free of side effects. These observations are of interest, since an analgesic with such attributes would have widespread clinical application. This study was undertaken in an effort to appraise the effect of dihydrocodeine upon respiration and circulation in man.

METHODS

An initial clinical evaluation of the analgesic powers of dihydrocodeine suggested to us that 30 mg. of dihydrocodeine were not equivalent to 10 mg. of morphine. These observations were made in the recovery room in patients experiencing acute postoperative pain. Because of this observation and since we were dealing with healthy, young males, we decided to administer a higher dose of the drug than advised as optimal (5). Therefore, 50 or 60 mg. of dihydrocodeine were injected intramuscularly in all subjects except one who received 75 mg.

The effect of dihydrocodeine upon respiration was studied in normal, 20 to 30-year-old men volunteers. The method employed has been described in detail (2) and consisted of a closed, carbon dioxide-absorption breathing system incorporating a 6-liter recording spirometer and an infrared carbon dioxide analyzer. Control observations were made of respiratory rate, tidal volume, and end-expiratory carbon dioxide concentration. Minute volume of respiration and pCO_2 were calculated. The respiratory response to endogenously accumulated carbon dioxide (soda lime canister shunted out of the system) was then measured (2). Similar measurements were made after the administration of dihydrocodeine.

The effect of dihydrocodeine upon circulation was studied in the same group of subjects and in additional males in the same age range. Blood pressure and heart rate were obtained by the use of an intra-arterial capacitance manometer. The effect of a 50 to 60 degree head-

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up tilt was studied in 10 of these subjects. The duration of the tilt was fifteen minutes unless severe hypotension or fainting occurred, at which time the subject was promptly returned to the horizontal position.

Results

The effect of dihydrocodeine upon respiration and the respiratory response to endogenously accumulated carbon dioxide can be seen in table 1. In all 5 subjects, there was a rise in end-expiratory carbon dioxide tension of from 2 to 6 mm. of mercury. Respiratory rate like-

TABLE 1

The Effect of Dihydrocodeine Upon Respiration

		Control Readings	CO_2	Control Readings	CO_2	Control Readings	CO_2	Control Readings	CO_2
		Control		45 minutes		85 minutes		150 minutes	
B. M., Male, 26 yrs.	pCO_2	43	64	44	65	45	64	39	64
Ht. 71", Wt. 175 lbs.	R. R.	11	14	8	14	9	14	6	14
Dihydrocodeine	T. V.	520	2580	640	2960	640	3000	1160	2480
(60 mg.)	M. V.	5.7	36.1	5.1	41.5	5.8	44.5	7.0	34.7
		Control		35 minutes		80 minutes		160 minutes	
C. R., Male, 27 yrs.	pCO_2	42	64	45	63	46	65	44	63
Ht. 73", Wt. 145 lbs.	R. R.	11	16	10	12	11	15	11	20
Dihydrocodeine	T. V.	510	1660	460	1220	420	1160	480	1540
(60 mg.)	M. V.	5.5	26.6	4.6	14.6	4.6	17.40	5.3	30.8
		Control		36 minutes		75 minutes		130 minutes	
K. D., Male, 25 yrs.	pCO_2	35	59	39	60	39	60	41	61
Ht. 72", Wt. 188 lbs.	R. R.	21	19	19	29	18	23	19	21
Dihydrocodeine	T. V.	420	2400	410	2000	400	2120	400	1880
(60 mg.)	M. V.	8.3	45.7	7.9	48.5	7.2	48.6	7.6	39.6
		Control		50 minutes		105 minutes			
A. H., Male, 25 yrs.	pCO_2	40	65	45	66	42	66		
Ht. 66", Wt. 125 lbs.	R. R.	8	9	6	10	10	9		
Dihydrocodeine	T. V.	510	2610	720	2560	450	2410		
(50 mg.)	M. V.	4.1	23.5	4.3	25.6	4.5	21.7		
		Control		30 mintues		60 minutes		120 minutes	
W. G., Male, 24 yrs.	pCO_2	38.5	58	42	59	41	58	40	58.5
Ht. 72", Wt. 165 lbs.	R. R.	13	18	12	20	12	16	12	16
Dihydrocodeine	T. V.	520	2300	440	1660	450	2400	460	2230
(60 mg.)	M. V.	6.6	41.4	5.2	33.2	5.4	35.5	5.5	35.6

CO_2—response to endogenously accumulated carbon dioxide.
R. R.—respiratory rate per minute.
T. V.—respiratory tidal volume in cubic centimeters.
M. V.—respiratory minute volume liters per minute.

TABLE 2

THE EFFECT OF DIHYDROCODEINE UPON CIRCULATION AS DETERMINED BY THE 50 TO 60 DEGREE HEAD-UP TILT

Subject	Control													
			Tilt								Flat			
	Control		1 minute		5 minutes		10 minutes		15 minutes		1 minute after		2 minutes after	
	Blood Pressure (mm. Hg)	Pulse (beats/ minute)	Blood Pressure (mm. Hg)	Pulse (beats/ minute)	Blood Pressure (mm. Hg)	Pulse (beats/ minute)	Blood Pressure (mm. Hg)	Pulse (beats/ minute)	Blood Pressure (mm. Hg)	Pulse (beats/ minute)	Blood Pressure (mm. Hg)	Pulse (beats/ minute)	Blood Pressure (mm. Hg)	Pulse (beats/ minute)
A. H.	110/70	82	104/64	92	92/56	96	100/58	88	100/60	88	122/64	86	112/60	86
K. C.	108/66	72	94/60	88	96/64	100	98/64	104	96/64	104	108/64	64	116/68	64
R. G.	114/76	62	96/70	78	92/70	72	92/68	72	92/68	68	100/70	64	108/76	56
W. M.	110/80	70	92/76	88	90/68	86	80/68	110	52/48 Faint—12 minutes	120	96/60	80	108/72	60
C. R.	108/60	72	92/64	88	100/64	88	110/70	88	108/88	88	120/60	72	120/60	72
R. C.	100/60	78	84/60	84	76/56	80	80/56	84	70/54	80	100/70	64	92/68	64
P. A.	115/60	70	115/70	72	108/68	78	115/70	72	65/40	66	90/55	66	110/70	54

TABLE 2—(*Continued*)

Subject	Dihydrocodeine (mg.)	Minutes after Drug	Test													
					Tilt								Flat			
			Control		1 minute		5 minutes		10 minutes		15 minutes		1 minute		2 minutes	
			Blood Pressure (mm. Hg)	Pulse (beats/minute)	Blood Pressure (mm. Hg)	Pulse (beats/minute)	Blood Pressure (mm. Hg)	Pulse (beats/minute)	Blood Pressure (mm. Hg)	Pulse (beats/minute)	Blood Pressure (mm. Hg)	Pulse (beats/minute)	Blood Pressure (mm. Hg)	Pulse (beats/minute)	Blood Pressure (mm. Hg)	Pulse (beats/minute)
A. H.	50	64	108/58	80	100/60	96	96/58	96	92/58	88	92/58	86	108/56	72	112/64	66
K. C.	60	44	110/68	62	104/70	86	100/68	80	92/64	80	36/24 Faint—12 minutes	56	100/68	66	104/64	64
R. G.	60	44	100/72	54	92/68	72	90/66	64	50/30 Faint—9 minutes	40	Faint—9 minutes		80/54	60	96/68	46
W. M.	60	45	116/82	60	100/76	80	96/76	76	96/70	76	90/68	76	92/78	76	108/70	68
C. R.	60	52	100/52	72	94/60	88	100/58	100	48/38 Faint—9 minutes	60	Faint—9 minutes		88/40	56	108/54	56
R. C.	75	44	102/66	72	88/64	88	88/64	90	80/56	88	84/56	80	92/56	76	100/60	68
P. A.	50	43	110/68	78	105/70	78	100/70	78	90/60	78	60/40	66	92/55	60	98/60	60

wise decreased in all 5 subjects, but not remarkably so. The change in tidal volume was variable and minimal, increasing in 2 subjects and decreasing in 3. The respiratory minute volume diminished in 4 of the 5 subjects.

The peak respiratory response to endogenously accumulated carbon dioxide appeared unchanged after dihydrocodeine in 2 subjects, elevated in one subject, and depressed in the remaining 2. All subjects, however, demonstrated a slightly depressed minute volume response to carbon dioxide in the ranges of 50 to 55 mm. of mercury tension.

The effect of dihydrocodeine upon the circulatory response to tilting was observed in 10 subjects. Data from 7 of these subjects are presented (table 2). Observations from 3 subjects have been deleted. One individual became hypotensive and felt faint twice following control tilts of five and one-half minutes. Forty-five minutes following dihydrocodeine (50 mg.), he complained of nausea and feeling of faintness four and one-half minutes after tilting. Questioning revealed that this subject had fainted several times while standing at attention in the service. He had learned to keep his legs moving to prevent fainting while standing. The other 2 individuals omitted likewise fainted on control and test tilts. Both experienced severe pain at the site of the arterial puncture on the control tilt. We believed this to have played a part in precipitating hypotension and fainting. Neither subject complained of pain with the tilt after dihydrocodeine. Fainting occurred at two and six minutes on the control tilt and eleven and nine minutes on the test tilts respectively.

In the data from the remaining 7 subjects, one individual fainted during the control tilt. After the drug, 3 subjects became hypotensive and fainted. The subject who fainted during the control tilt did not faint during the test tilt. In 6 of the 7 subjects, pulse rate tended to increase during the tilt after dihydrocodeine. In the 3 subjects who fainted, a bradycardia occurred at the time of the faint.

Discussion

These investigations suggest that dihydrocodeine in the doses used has a slight respiratory depressant effect which is less, however, than that observed with a series of well-known opiate and opiate-like drugs (3). The respiratory response was less than that observed in two subjects following the intramuscular injection of 60 mg. of codeine sulfate (3).

The depressant effect appeared less prominent if the respiration was stimulated with high carbon dioxide tension, but was apparent with carbon dioxide tensions in the range of 50 to 55 mm. of mercury. The significance of this observation is uncertain. In large doses, dihydrocodeine stimulates the central nervous system, occasionally causing convulsions (4). High levels of carbon dioxide might conceivably potentiate such a stimulant action.

Dihydrocodeine predisposed to hypotension as evidenced by the tilt test. The fact that 3 out of 7 subjects fainted following tilt would suggest this drug is not very different from morphine in its effect upon the circulation (1). Indeed, if one compares the 8 patients in the same age group reported by Drew, Dripps, and Comroe (1), all of whom received 20 mg. of morphine, dihydrocodeine appears to have a greater effect upon the circulation than does morphine. In Drew's group, 2 of 8 patients fainted while in our group, 3 of 7 fainted.

We are not able to discuss the comparative analgesic potency of morphine and dihydrocodeine. Our initial observations suggest that a 30 mg. dose of dihydrocodeine does not approach 10 mg. of the former in analgesic potency. We have begun a series of observations in patients with immediate postoperative pain, and will report our findings at a later date. If the resulting analgesia proves to be within the same range as that produced by commonly administered doses of morphine, dihydrocodeine would appear to have advantages. The fact that the drug depresses respiration to a negligible extent and its effect upon the circulation is approximately the same as morphine, might make dihydrocodeine the drug of choice for analgesia in postoperative patients.

Summary

The effect of dihydrocodeine upon the respiration and circulation of man has been investigated. Fifty to 60 mg. of dihydrocodeine produced a slight depression of respiration, but did not influence the respiratory response to the peak endogenous accumulation of carbon dioxide. The same doses led to fainting in 3 of 7 normal individuals when subjected to a 50 to 60 degree head-up tilt.

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