

CIRCULATORY EFFECTS OF CHLORPROMAZINE BEFORE AND DURING CYCLOPROPANE ANESTHESIA IN MAN

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CHLORPROMAZINE (Thorazine®)* has been considered as a useful pre-anesthetic drug because of its sedative, drying, and antiemetic effect and its probable potentiation of anesthetic agents (1-7). However, hypotension, tachycardia, and refractory responsiveness to pressor agents have been regarded as its undesirable side effects (8, 9, 10). Changes in position, administration of a barbiturate, and spinal anesthesia have caused precipitous fall in blood pressure in patients with chlorpromazine premedication (11-14).

The considerations concerned with the blood pressure and changes in cardiac rate were based upon clinical studies, and it was realized that a quantitative determination of the effect of this drug upon the circulation was needed. This study was, therefore, undertaken to determine the time of onset, the magnitude and the duration of action of chlorpromazine upon the cardiac output, direct arterial pressure, heart rate, total peripheral resistance, intrathoracic blood volume, stroke volume, and left ventricular work following its administration and during cyclopropane anesthesia. These changes in cardio-hemodynamics during chlorpromazine and cyclopropane anesthesia were compared with the changes when morphine and scopolamine were used for premedication.

METHOD

Two groups of patients were studied prior to surgery. Thirty-eight determinations of the cardiac output and related hemodynamics were obtained in one group of 14 patients (average age: 51 years) before and after the intravenous administration of chlorpromazine. In 7 patients, cyclopropane was administered 60 minutes after the intravenous administration of chlorpromazine and the hemodynamic studies were continued during cyclopropane anesthesia (electroencephalographic level II to III, blood cyclopropane concentration 5-15 mg. per cent).

Thirty-five determinations of the cardiac output and related hemodynamics were obtained in a second group of 14 subjects (average age:

Read before the annual meeting of the American Society of Anesthesiologists in Kansas City, Missouri, October 11, 1956. Accepted for publication November 20, 1956. The authors are in the Department of Anesthesiology, New England Center Hospital and Department of Surgery (Anesthesia), Tufts University School of Medicine, Boston, Massachusetts. The work was aided by a research grant from the National Institutes of Health, Public Health Service No. H-1711 (C4).

* Supplied by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

43 years) 60 minutes after the subcutaneous administration of 5.5 to 10.0 mg. of morphine sulfate and 0.3 to 0.4 mg. of scopolamine and during cyclopropane anesthesia (electroencephalographic level II to III, blood cyclopropane concentration 5–15 mg. per cent).

The subjects in both groups were in good physical condition and had no discernible cardiovascular or pulmonary disease (except one case with essential hypertension). The patients were placed in the supine position in a quiet room for study. A 15 gauge needle was inserted in the median basilic vein of one arm elevated above the angle of Louis for the administration of drugs. A thin-walled 18 gauge needle was inserted into the brachial artery of the other arm for pressure measurements and for the collection of blood samples. Electrocardiographic and electroencephalographic electrodes were appropriately positioned (15).

After a steady resting state was maintained for at least 30 minutes, the following observations were made: cardiac output, arterial blood pressure, heart rate, total peripheral resistance, stroke volume, mean circulation time, intrathoracic blood volume, blood oxygen content and capacity, carbon dioxide content, and *pH*. Chlorpromazine (2.5 per cent concentration) was administered intravenously (from 0.3 to 1.2 mg. per kg. body weight) at a rate of 1 cc. per 5 seconds. The cardiac output and the blood gases were determined at specific intervals 15, 30 and 60 minutes after the administration of the drug. Each patient served as his own control and the findings were compared with those obtained during the resting state.

The cardiac output was determined by the modified dye dilution method; the injection of the dye, collection of arterial blood samples, and calculation of the cardiac output values were carried out according to the procedures described previously (16, 17, 18). The electroencephalogram, electrocardiogram, and brachial arterial pressure (via Statham strain gauge, Model P23A) were simultaneously and continuously recorded on a multichannel, direct writing oscillograph with a frequency response of 60 cycles per second. The mean arterial pressure was determined by planimetry of the pulse wave. Samples of arterial blood were drawn, immediately before determination of cardiac output, for analysis of oxygen content and capacity, carbon dioxide content and *pH* (blood gases by Van Slyke and *pH* by Cambridge Electron Ray *pH* meter—Research Model). Values of the *pH* were accepted when the duplicates checked within 0.02 unit. The carbon dioxide tension was calculated from the carbon dioxide serum content and *pH* values by means of the nomogram of Peters and Van Slyke (19). The hematocrit was determined by centrifuging the heparinized blood in Wintrobe tubes.

Oxygen was given for at least 15 minutes before the administration of cyclopropane by means of the conventional to-and-fro absorption technique. The various levels of surgical anesthesia were classified

according to both electroencephalographic level (15) and the concentration of blood cyclopropane, which was determined by the method of Oreutt and Waters (20).

The intrathoracic blood volume (or central blood volume), the mean circulation time, total peripheral resistance, and left ventricular work were calculated according to the conventional formulas (21).

TABLE 1
SUMMARY OF HEMODYNAMIC CHANGES RELATED TO INTRAVENOUS CHLORPROMAZINE

	Resting State (Absolute Values)	Per Cent Change: After Administration of Chlorpromazine Intravenously			
		1-15 Minutes	16-30 Minutes	31-90 Minutes	
Cardiac index (l/min./m ² .)	3.37 ±0.2* ±0.7†	+13 ±7 ±20	-3 ±5 ±13	-12 ±6 ±13	
Arterial P _m (mm. Hg)	103 ±4 ±14	-14 ±1 ±4	-13 ±4 ±10	-17 ±8 ±16	
Heart rate (per minute)	71 ±3 ±10	+17 ±5 ±12	+23 ±13 ±31	+29 ±14 ±29	
Total peripheral resistance (dynes-sec.-cm. ⁻⁵)	1580 ±150 ±500	-20 ±7 ±17	-8 ±10 ±23	-18 ±7 ±14	
Stroke volume index (cc./beat/m ² .)	47 ±3 ±11	-4 ±8 ±20	-14 ±6 ±13	-16 ±12 ±24	
Mean circulation time (sec.)	21 ±1 ±3	-2 ±12 ±31	-11 ±10 ±22	+13 ±10 ±21	
Intrathoracic blood volume index (l/m ²)	1.20 ±0.1 ±0.2	+8 ±13 ±32	-10 ±9 ±21	-4 ±7 ±15	
Left ventricular work (kg.-meters/min.)	8.0 ±0.8 ±2.7	-4 ±7 ±18	-12 ±5 ±12	-38 ±10 ±17	

* Standard error

† Standard deviation

RESULTS

The pertinent data before and after the intravenous administration of chlorpromazine are summarized in table 1. The per cent change refers to the mean per cent change of each group of determinations obtained from 1 to 15 minutes, 16 to 30 minutes and 31 to 90 minutes after the intravenous administration of chlorpromazine. The hemodynamic changes observed during cyclopropane anesthesia in the group of patients premedicated with morphine-scopolamine were compared with the values obtained in the chlorpromazine premedicated subjects during cyclopropane anesthesia (table 2).

Cardiac Index.—The mean cardiac index during the resting state prior to the administration of chlorpromazine was 3.37 l./min./m.² and

the standard deviation of the sample was ± 0.67 l./min./m.² The average per cent change of the cardiac index obtained within 15 minutes after the administration of the drug was 13 per cent ($P > 0.05$) higher than the resting value. Within this period of time the cardiac index was unaltered in three instances. It was reduced 21 per cent in one instance, and it was increased in the remaining three + 21, + 37 and + 41 per cent. In the groups of observations obtained 30 minutes and 60 minutes after the administration of the drug, the average cardiac

TABLE 2

EFFECT OF MORPHINE AND SCOPOLAMINE COMPARED WITH CHLORPROMAZINE PREMEDICATION UPON THE HEMODYNAMIC CHANGES DURING CYCLOPROPANE ANESTHESIA*

	Morphine and Scopolamine (Absolute Values)	Cyclopropane Anesthesia (% Change)	Chlorpromazine (Absolute Values)	Cyclopropane Anesthesia (% Change)
Cardiac index (l./min./m. ²)	3.32 ± 0.18 † ± 0.67 ‡	-18 ± 6 ± 17	3.17 ± 0.17 ± 0.43	+7 ± 5 ± 14
Heart rate per minute	67 ± 2 ± 7	-17 ± 3 ± 8	82 ± 8 ± 19	-7 ± 8 ± 21
Stroke volume index (cc./beat/m. ²)	50 +3 ± 10	-2 ± 7 ± 18	40 ± 2 ± 5	+24 ± 13 ± 33
Intrathoracic blood volume index (l./m. ²)	1.0 ± 0.1 ± 0.3	-8 ± 7 ± 18	1.1 ± 0.1 ± 0.2	+6 ± 9 ± 23
Arterial P _m (mm. Hg)	95 ± 4 ± 16	+17 ± 4 ± 10	87 ± 5 ± 12	+11 ± 7 ± 18
Total peripheral resistance (dynes-sec.-cm. ⁻⁵)	1600 ± 130 ± 500	+46 ± 10 ± 27	1200 ± 140 ± 340	+12 ± 9 ± 25
Left ventricular work (kg.-meters/min.)	6.7 ± 0.4 ± 1.5	-4 ± 9 ± 23	7.5 ± 1.4 ± 3.4	+8 ± 11 ± 27
Mean circulation time (sec.)	17 ± 1 ± 4	+27 ± 12 ± 31	22 ± 2 ± 5	± 0 ± 11 ± 31

* Cyclopropane anesthesia was maintained at an electroencephalographic level II to III in both series of experiments.

† Standard error.

‡ Standard deviation.

index was - 2 per cent ($P > 0.1$) and - 12 per cent ($P > 0.1$) respectively, as compared with the resting value (table 1). These changes are not statistically significant.

In the group of patients with chlorpromazine premedication the cardiac index increased 7 per cent ($P > 0.1$) during cyclopropane anesthesia (electroencephalographic level II to III). In the other group of patients premedicated with morphine-scopolamine the average change of the cardiac index during cyclopropane anesthesia was - 18 per cent ($P < 0.001$ —table 2).

Arterial Blood Pressure.—The average value of the mean arterial blood pressure during the resting state prior to the administration of chlorpromazine was 103 mm. of Hg (standard deviation: ± 15). After the administration of the drug, in all instances, the blood pressure fell

and the time of onset varied from 15 seconds to 2 minutes. The average drop of the mean arterial blood pressure during the first 15 minutes was -14 per cent ($P < 0.001$), within 30 minutes was -13 per cent ($P > 0.05$) and after 90 minutes -17 per cent ($P < 0.05$). However, the per cent fall (from -10 to -60 per cent) and the duration (from 2 to 20 minutes) of the mean arterial blood pressure varied from patient to patient. In two subjects, one hypertensive and the other normotensive, the decrease in blood pressure persisted for two and one-half hours (-50 per cent and -40 per cent). The per cent drop in mean arterial blood pressure was plotted against the intravenous dosage of chlorpromazine in mg. per kg. body weight given at a rate of 25 mg. per 5 seconds. There was no relationship between the percentage drop of blood pressure and the dosage (fig. 1a).

During cyclopropane anesthesia (electroencephalographic level II to III) in the subjects with chlorpromazine premedication the average per cent change of the mean arterial blood pressure was $+11$ per cent ($P > 0.1$), and in the patients with morphine-scopolamine premedication the average percentage change of the mean arterial blood pressure was $+17$ per cent ($P < 0.001$) (table 2).

Heart Rate.—The mean heart rate during the resting state was 71 beats per minute (standard deviation: ± 11). The average change of the heart rate was $+17$ per cent ($P < 0.02$) (range from $+3$ to $+39$ per cent) within 15 minutes after the administration of chlorpromazine; within 30 minutes it was $+23$ per cent ($P > 0.1$) (range from -8 to $+79$ per cent); and within 90 minutes it was $+29$ per cent ($P > 0.1$) (range from 0 to $+78$ per cent). There was no relationship between the per cent change of heart rate and the dosage (fig. 1b).

The average change of the heart rate was -7 per cent ($P > 0.5$) during cyclopropane anesthesia in the patients with chlorpromazine premedication. Of this group the heart rate was increased in one instance ($+23$ per cent); and in all the others there was either no change or a decrease. The average change of the heart rate was -16 per cent ($P < 0.001$) during cyclopropane anesthesia in the patients with morphine-scopolamine premedication (table 2).

Stroke Volume Index.—The mean stroke volume index during the resting state before the administration of chlorpromazine was 47 cc./beat/m.² with a standard deviation of ± 11 . The average per cent change of the stroke volume index obtained within 15, 30 and 90 minutes after the administration of the drug was -4 per cent ($P > 0.1$), -14 per cent ($P > 0.05$) and -16 per cent ($P < 0.1$) respectively.

The average per cent change of the stroke volume was not statistically significant during cyclopropane anesthesia in the patients with chlorpromazine premedication ($P = 0.1$) and in the patients with morphine-scopolamine premedication ($P > 0.05$ —table 2).

Total Peripheral Resistance.—The mean value of the total peripheral resistance during the resting state was 1,600 absolute units with a

TABLE 3

AVERAGE VALUES OF ARTERIAL $p\text{CO}_2$ AND O_2 SATURATION FROM EIGHT EXPERIMENTS BEFORE AND FOLLOWING INTRAVENOUS CHLORPROMAZINE

	Resting State	Minutes after Chlorpromazine		
		1-15	16-30	31-90
$p\text{CO}_2$ (mm. Hg)	40	40	47	43
O_2 Sat. (%)	93	95	95	95

standard deviation of ± 500 . The average per cent change of the total peripheral resistance obtained within 15, 30 and 90 minutes was -20 per cent ($P < 0.02$), -8 per cent ($P > 0.1$), and -18 per cent ($P < 0.05$) respectively. Within 15 minutes after the administration of chlorpromazine 5 out of the 6 determinations showed a reduction from 12 to 41 per cent.

During cyclopropane anesthesia the average change of the total peripheral resistance was $+12$ per cent ($P > 0.1$) in the subjects with chlorpromazine premedication and was $+46$ per cent ($P < 0.001$) in the subjects with morphine-scopolamine premedication (table 2).

Mean Circulation Time.—The average mean circulation time during the resting state was 21 seconds (standard deviation: ± 3). Within 15, 30 and 90 minutes after the administration of chlorpromazine the changes were not statistically significant ($P > 0.1$ —table 2).

During cyclopropane anesthesia the average change of the mean circulation time was not significant in the chlorpromazine sedated patients ($P > 0.1$). In the subjects with morphine-scopolamine premedication the average change was $+27$ per cent ($P < 0.001$ —table 2).

Intrathoracic Blood Volume.—The mean value of the intrathoracic blood volume index during the resting state was 1.12 l./m.^2 and there was no significant change ($P > 0.1$) after the administration of chlorpromazine and during cyclopropane anesthesia with both types of premedication.

Left Ventricular Work.—The mean value of the left ventricular work during the resting state was $8.0 \text{ kg.-meters per minute}$. Within 15, 30 and 60 minutes after intravenous chlorpromazine the average drop of left ventricular work was -4 per cent ($P > 0.1$), -12 per cent ($P > 0.5$) and -38 per cent ($P < 0.02$). During the cyclopropane anesthesia following chlorpromazine premedication, the left ventricular work was $+8$ per cent ($P > 0.1$ —table 1). In the patients with morphine-scopolamine premedication during cyclopropane anesthesia the average change of the left ventricular work was -4 per cent ($P > 0.5$ —table 2).

$p\text{CO}_2$ and O_2 Saturation.—The mean value of the arterial $p\text{CO}_2$ during the resting state was 40 mm. of Hg , and there was no significant change after the administration of chlorpromazine (table 3).

The mean value of the oxygen saturation of the arterial blood during the resting state was 93 per cent, and there was no significant change after the administration of chlorpromazine (table 3).

Variations of the Hemodynamic Changes following Intravenous Chlorpromazine.—The following experiments (figs. 2 to 6) are presented to show the variable hemodynamic responses to single and repeated doses of chlorpromazine.

Figure 2 illustrates the immediate onset of hypotension in a 62-year-old male, 73 kg., with a resting blood pressure of 175/90. Ten seconds after the first administration of 25 mg. of chlorpromazine the

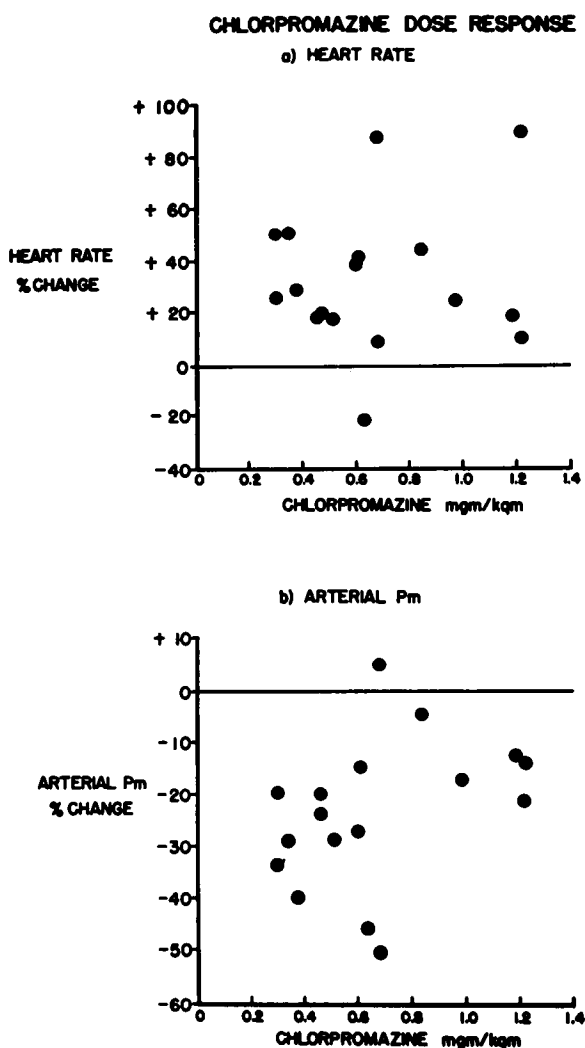


FIG. 1a AND b. The per cent changes of (a) heart rate and (b) mean arterial blood pressure were plotted against different dosages of chlorpromazine given intravenously in patients. No definite relationship was found.

blood pressure fell to 125/60 and subsequently to 85/40 within 40 seconds. Within 30 minutes the blood pressure returned to the control level. Thirty-five minutes later a second dose of 25 mg. was given and the blood pressure fell to 100/40 within 30 seconds, and gradually returned to the original level of 190/70 within 10 minutes. The heart rate increased from 72 to 90 per minute within 5 minutes after the first dose. Following the second dose the heart rate increased to 115 per minute within 20 seconds and persisted for 30 minutes.

Figure 3 illustrates hypotension of short duration, prolonged tachycardia, and a moderate degree of tachyphylaxis following repeated doses of chlorpromazine. Twenty-five milligrams of chlorpromazine

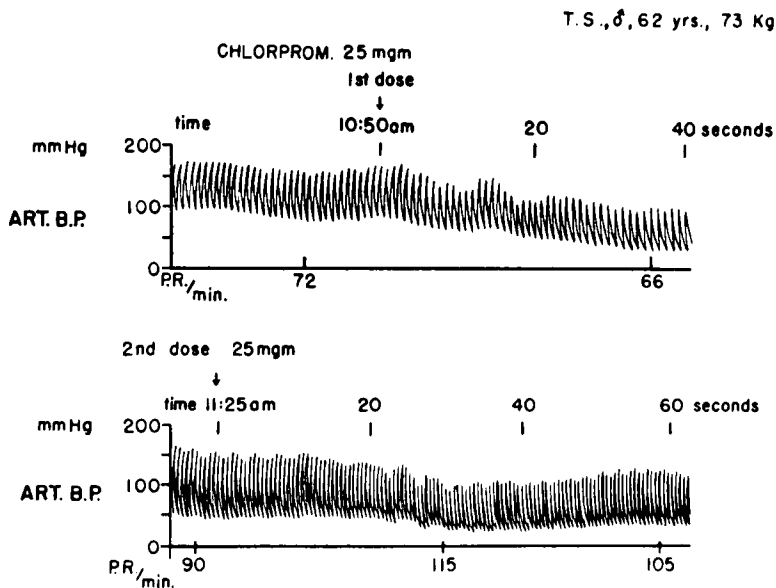


FIG. 2. Onset of hypotension in a 62-year-old male after intravenous chlorpromazine, showing arterial blood pressure and heart rate.

was given intravenously to a 40-year-old normotensive female. Within 30 seconds the blood pressure fell from 125/75 to 110/60 and within two minutes dropped further to 90/50. After one minute the blood pressure returned to the control level of 120/65. Seven minutes after the first dose, a second dose of 25 mg. was given. Within 20 seconds there was a slight drop in systolic and diastolic blood pressure which lasted for 30 seconds. Then three minutes after the second dose a third dose of 25 mg. was given. There was no significant change in blood pressure. The period of transient hypotension shown in the bottom tracing was related to yawning. The increase in pulse rate from 66 to 156 occurred two minutes after the administration of the drug, persisted for one minute and remained within the range of 84 to 114 per minute.

Repeated doses caused a slight increase in heart rate lasting for one minute.

Figure 4 illustrates the blocking effect of chlorpromazine on the peripheral pressor reflexes after the intravenous administration of 40 mg. chlorpromazine. Although the arterial blood pressure returned to the control level after the intravenous administration of 40 mg. of chlorpromazine, the blood pressure overshoot following the Valsalva

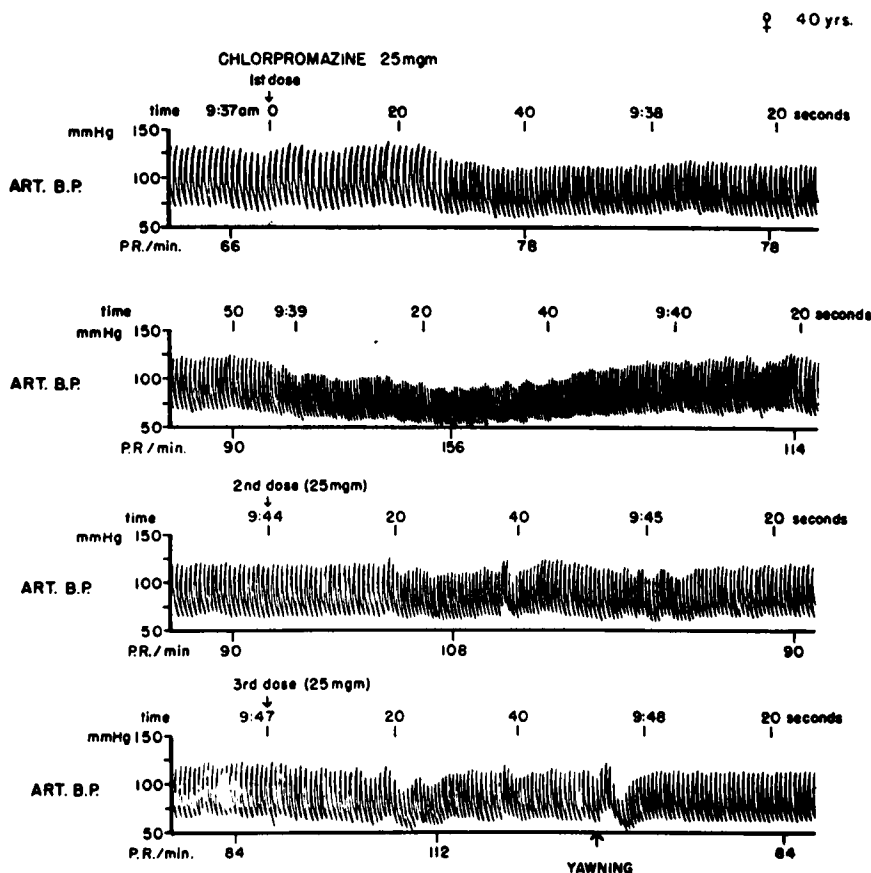


FIG. 3. Hypotension of short duration, prolonged tachycardia, and a moderate degree of tachyphylaxis following repeated doses of intravenous chlorpromazine.

maneuver did not occur. Thus, the blood pressure within normal levels following the administration of chlorpromazine does not indicate the duration of the action of this drug upon the peripheral circulation.

Figure 5 illustrates the blood pressure and changes in heart rate during cyclopropane anesthesia in a patient with chlorpromazine premedication. Fifteen minutes after the administration of chlorpromazine the blood pressure fell from 120/65 to 70/45 mm. of Hg. It gradually returned to 85/50 in the next 15 minutes. At this time anesthesia

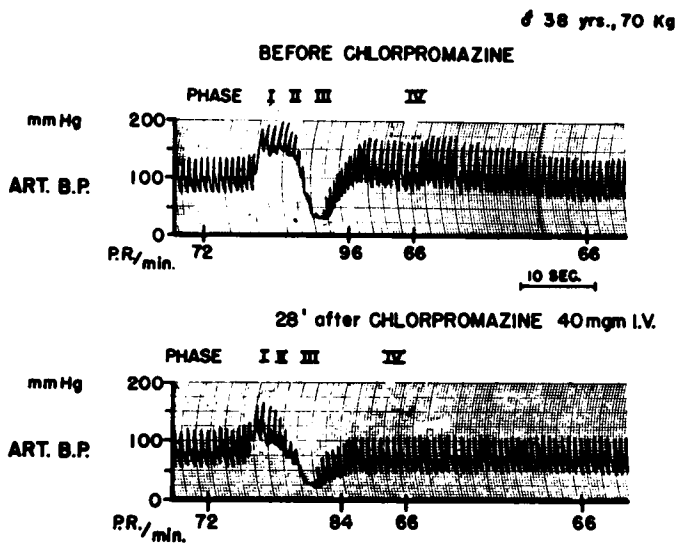


FIG. 4. Blocking effect of chlorpromazine on peripheral pressor reflexes after intravenous control level, the blood pressure overshoot following the Valsalva maneuver did not occur.

was induced with cyclopropane. Within 15 minutes the blood pressure rose to 118/60 mm. of Hg and subsequently remained at 100/60 mm. of Hg. The most striking change was the reduction in the pulse pressure after the administration of chlorpromazine from 55 to 25 mm. of Hg and the prompt return of the pulse pressure during anesthesia from 25 mm. of Hg to 45 mm. of Hg. The cardiac rate increased from

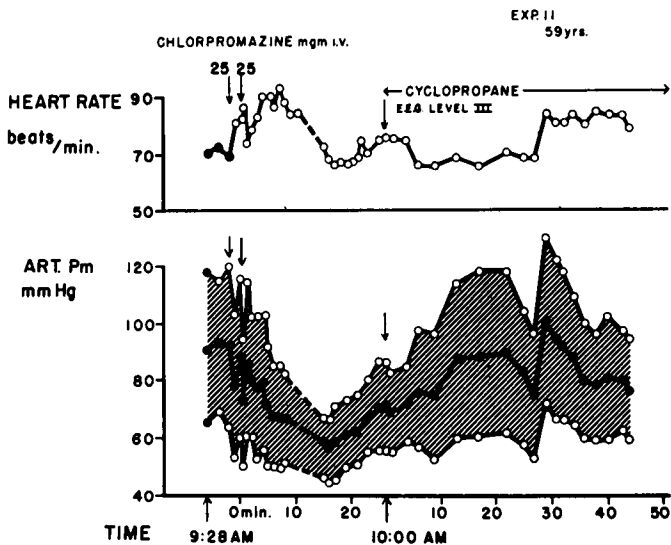


FIG. 5. The blood pressure and changes in heart rate during cyclopropane anesthesia in a patient with chlorpromazine premedication.

70/minute to 90/minute for 20 minutes after 50 mg. of intravenous chlorpromazine. During anesthesia the rate ranged from 68 to 85 beats per minutes.

DISCUSSION

Following the intravenous administration of chlorpromazine, the cardiac output remained constant and within control levels except for a transient rise that occurred within the first 15 minutes. This occasional rise of the cardiac output was not a constant finding and not statistically significant. The cardiac output also remained unchanged during cyclopropane anesthesia when chlorpromazine was used for premedication. This response was in contrast to the 18 per cent reduction of the cardiac output during cyclopropane anesthesia when morphine and scopolamine were used as premedicants. The reduction of the cardiac output during cyclopropane anesthesia with morphine-scopolamine premedication was attributed to the decrease in heart rate and to the elevation in total peripheral resistance (22). These changes were minimal in the patients with chlorpromazine premedication during cyclopropane anesthesia.

The reduction of the total peripheral resistance was prolonged and occurred within the first 5 minutes following the administration of chlorpromazine. This was most likely the cause for the reduction of the arterial blood pressure since the cardiac output was unaltered. The decrease in total peripheral resistance in part may explain the untoward circulatory response when this drug is used with pentothal anesthesia, spinal or epidural anesthesia, or splanchnic block (11-14).

The time of onset, duration and magnitude of the fall in blood pressure and the increase in heart rate varied from patient to patient and were not related to the doses of chlorpromazine (fig. 1a and 1b). The most pronounced change in blood pressure occurred following the first dose of the drug and with subsequent similar doses the reduction of the blood pressure was slight. This phenomenon of tachyphylaxis occurred in most instances.

The duration of either the adrenergic or ganglionic blocking effect of chlorpromazine lasted longer than the period of hypotension. This was shown by the obliteration of the blood pressure overshoot following a Valsalva maneuver after the blood pressure had returned to the control level. Therefore, it appears that the blood pressure should not be taken as a guide concerning the duration of the action of the drug.

The use of morphine and scopolamine for premedication served as a basis to compare the effects of chlorpromazine during cyclopropane anesthesia. When chlorpromazine was used, the slowing of the heart rate and the elevation of the blood pressure were not observed during varying levels of cyclopropane anesthesia. This is in contrast to the changes of the heart rate and blood pressure during cyclopropane anesthesia when morphine-scopolamine was used as a premedicant.

The use of chlorpromazine as a premedicant for cyclopropane anesthesia revealed no untoward circulatory effects. Indeed, the arterial blood pressure and total peripheral resistance were either unchanged or elevated during cyclopropane anesthesia (electroencephalographic level II to III) in the subjects with chlorpromazine premedication. The pressor effect of cyclopropane (22) may account for the maintenance of the blood pressure under these conditions.

SUMMARY

The intravenous administration of chlorpromazine (0.3 to 1.2 mg./kg. body weight) caused no significant change of the cardiac output but a consistent reduction of the total peripheral resistance. In most instances there was a drop in blood pressure and an increase of the heart rate. The time of onset, duration and magnitude of these changes varied from patient to patient and were not correlated with the dosage. During cyclopropane anesthesia in the patients with chlorpromazine premedication the total peripheral resistance and arterial blood pressure were either unchanged or slightly elevated and the cardiac output remained at the control level. These hemodynamic changes were not similar to those observed when morphine-scopolamine was used as premedication. No untoward circulatory effects were observed when chlorpromazine was used as a premedicant for cyclopropane anesthesia.

REFERENCES

1. Woodbridge, P. D.: Postanesthetic Vomiting, *J. A. M. A.* **161**: 644 (June 16) 1956 (correspondence).
2. Dobkin, A. B., Wehling, B., Gross, G., and Mendelsohn, H.: Chlorpromazine in Anesthesia; for Surgical Treatment of Pulmonary Tuberculosis, *Anesthesia* **10**: 328 (Oct.) 1955.
3. Friend, D. G., and Cummins, J. F.: Use of Chlorpromazine in Treatment of Nausea and Vomiting of Uremia, *New England J. Med.* **250**: 997 (June 10) 1954.
4. Albert, S. W., and Coakley, C. S.: Use of Chlorpromazine to Control Post-anesthetic Vomiting, *Anesth. & Analg.* **33**: 285 (July-Aug.) 1954.
5. Dobkin, A. B., Gilbert, R. G. B., and Lamoureux, L.: Physiological Effects of Chlorpromazine, *Anesthesia* **9**: 157 (July) 1954.
6. Sadove, M. S., Levin, M. J., Rose, R. F., Schwartz, L., and Witt, F. W.: Chlorpromazine and Narcotics in Management of Pain of Malignant Lesions, *J. A. M. A.* **155**: 626 (June 12) 1954.
7. Vandewater, S. L., and Gordon, R. A.: Largactil in Anaesthesia, *Canad. Anaesth. Soc. J.* **2**: 23 (Jan.) 1955.
8. Weiss, W. A., McGee, J. P., Jr., Branford, J. O., and Hanks, E. C.: Value of Chlorpromazine in Preoperative Medication, *J. A. M. A.* **161**: 812 (June 30) 1956.
9. Foster, C. A., O'Mullane, E. J., Gaskell, P., and Churchill-Davidson, H. C.: Chlorpromazine, Study of its Action on Circulation in Man, *Lancet* **1**: 614 (Sept. 25) 1954.
10. Moyer, J. H., Kent, B., Knight, R., Morris, G., Huggins, R., and Handley, C. A.: Laboratory and Clinical Observations on Chlorpromazine (SKF-2601-A); Hemodynamic and Toxicological Studies, *Am. J. M. Sc.* **227**: 283 (March) 1954.
11. Moore, D. C., and Bridenbaugh, L. D.: Chlorpromazine; Report of One Death and Eight Near Fatalities Following Its Use in Conjunction with Spinal, Epidural and Celiac Plexus Block, *Surgery* **40**: 543 (Sept.) 1956.
12. Gilbert, R. G. B., Dobkin, A. B., and Lamoureux, L.: Investigation of New Drugs, with Special Reference to Largactil (Chlorpromazine, Thorazine, R.P. 4560, M. and B. 2378, 2601A S.K.F.) as Example, *Canad. Anaesth. Soc. J.* **2**: 5 (Jan.) 1955.

13. Morris, G., Matthews, W., and Moyer, J.: Clinical Experience with Chlorpromazine in Spinal Anesthesia, *Anesth. & Analg.* **33**: 340 (Sept.-Oct.) 1954.
14. Dripps, R. D., Vandam, L. D., Pierce, E. C., Oech, S. R., and Lurie, A. A.: Use of Chlorpromazine in Anesthesia and Surgery, *Ann. Surg.* **142**: 774 (Nov.) 1955.
15. Possati, S., Faulconer, A., Jr., Bickford, R. G., and Hunter, R. C.: Electro-encephalographic Patterns during Anesthesia with Cyclopropane; Correlation with Concentration of Cyclopropane in Arterial Blood, *Anesth. & Analg.* **32**: 130 (March-April) 1953.
16. Hamilton, W. F., Riley, R. L., Attyah, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, J. W., Richards, D. W., Jr., Wheeler, N. C., and Witham, A. C.: Comparison of Fick and Dye Injection Methods of Measuring Cardiac Output in Man, *Am. J. Physiol.* **153**: 309 (May) 1948.
17. Etsten, B. E., and Li, T. H.: Determination of Cardiac Output by Dye Dilution Method; Modifications, Comparison with the Fick Method, and Application During Anesthesia, *ANESTHESIOLOGY* **15**: 217 (May) 1954.
18. Li, T. H., Fisher, J. H., and Etsten, B. E.: Determination of Cardiac Output by Dye Injection Method, *Bull. New England M. Cen.* **15**: 97 (Sept.) 1953.
19. Peters, J. P., and Van Slyke, D. A.: Quantitative Clinical Chemistry, Volume II, Methods, Baltimore, Williams & Wilkins Co., 1932.
20. Orcutt, F. S., and Waters, R. M.: Method for Determination of Cyclopropane, Ethylene and Nitrous Oxide in Blood with Van Slyke-Neill Manometric Apparatus, *J. Biol. Chem.* **117**: 509 (Feb.) 1937.
21. Etsten, B., and Li, T. H.: Hemodynamic Changes During Thiopental Anesthesia in Humans; Cardiac Output, Stroke Volume, Total Peripheral Resistance, and Intrathoracic Blood Volume, *J. Clin. Invest.* **34**: 500 (March) 1955.
22. Li, T. H., and Etsten, B.: Effect of Cyclopropane Anesthesia on Cardiac Output and Related Hemodynamics in Man, *ANESTHESIOLOGY* **18**: 15 (Jan.-Feb.) 1957.

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