Treatment of Acute Left-Sided Heart Failure with Intramuscular Injection of Chlorpromazine

Junichiro MIFUNE, M.D., Kizuku KURAMOTO, M.D., Keiji UEDA, M.D.,
Satoru MATSUSHITA, M.D., Iwao KUWAJIMA, M.D., Makoto SAKAI, M.D.,
Tsutomu IWASAKI, M.D., Hiroshi INOUE, M.D., Tatsuo
SHINAGAWA, M.D., and Mototaka MURAKAMI, M.D.

SUMMARY

Hemodynamic responses to intramuscular injection of 5 to 10 mg (average 8.5 mg) of chlorpromazine were assessed in 10 patients with acute left-sided heart failure (treated group). Left ventricular filling pressure, blood pressure, heart rate, and cardiac index were measured before the injection and for 6 hours thereafter. In 8 patients with heart failure, the same hemodynamic monitoring was performed without the injection of chlorpromazine (control group).

In treated group significant reduction of left ventricular filling pressure was observed at 5 min after the injection of chlorpromazine. Left ventricular filling pressure showed a peak reduction from an average of 27.2 to 18.8 mmHg (-30.8% , $p<0.001$) at 15 min, and a significant reduction persisted for 6 hours. At 15 min, mean blood pressure was reduced slightly (101 to 92 mmHg, -9.0% , $p<0.05$) and cardiac index tended to increase slightly (2.11 to 2.28 L/min/M², $+7.8\%$, NS). Heart rate was unchanged. Relief of symptoms of pulmonary congestion was also observed within 15 min. Improvement of symptoms of pulmonary congestion was more prominent particularly in 3 patients who had severe dyspnea and stridor. In control group, left ventricular filling pressure, blood pressure, and heart rate showed no significant change over 6 hours.

The present study suggested that intramuscular injection of chlorpromazine at the dosage of 5 to 10 mg showed rapid and marked clinical improvement without significant side effects and therefore its use may be indicated in patients with acute left-sided heart failure, especially in paroxysmal episodes.

Additional Indexing Words:

Vasodilator Hemodynamic effect Left ventricular filling pressure
Blood pressure Cardiac index Sedative effect

From the Department of Internal Medicine, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan.

Address for reprint: Junichiro Mifune, M.D., Department of Internal Medicine, Tokyo Metropolitan Geriatric Hospital, Sakae-cho 35, Itabashi-ku, Tokyo 173, Japan.

Received for publication June 20, 1978.

ACUTE left-sided heart failure is a frequent cause of death in patients with ischemic heart disease, hypertension, aortic valvular disease, or mitral regurgitation. A number of works have demonstrated the effectiveness of vasodilators such as phentolamine, sodium nitroprusside and nitroglycerin in the treatment of heart failure.¹⁾⁻⁴⁾ But these agents have not sedative effect which helps to eliminate restlessness, hyperventilation, or sensation of dyspnea of patients. It is well known that morphine is one of the most useful drugs in the treatment of paroxysmal episodes associated with heart failure.⁵⁾ The clinical benefits are often striking and appear rapidly by its vasodilating and sedative effects. However, its wide use as a common therapeutic agent is restricted in Japan because of the regulations for narcotics.

Chlorpromazine, one of the major tranquilizers, has a potent vasodilating effect in addition to sedative effect.⁶⁾ That beneficial vasodilating effect of chlorpromazine has been applied for cardiovascular disorders mainly to improve tissue perfusion in patients with cardiogenic shock following open heart surgery, acute myocardial infarction or pulmonary embolism.⁷⁾⁻⁹⁾

In this study, we have demonstrated the rapid and potent hemodynamic effects of chlorpromazine injected intramuscularly in patients with acute left-sided heart failure.

SUBJECTS AND METHODS

Ten patients, 1 man and 9 women, aged 67 to 87 (average 74.8) years, who were treated with chlorpromazine, constituted the treated group. They had clinical evidence of acute left-sided heart failure when admitted to the Coronary Care Unit. Five patients had acute myocardial infarction, 3 had chronic ischemic heart disease, and 2 had hypertensive heart disease. Chlorpromazine was injected intramuscularly in a single dose of 5 to 10 mg, averaging 8.5 mg.

Eight patients, 2 men and 6 women, aged 68 to 81 (average 74.7) years, who did not receive the injection of chlorpromazine on the day of investigation, constituted control group. The symptoms of heart failure in this group were stable and not so severe as treated group. Three patients had acute myocardial infarction, 4 had chronic ischemic heart disease, and 1 had hypertensive heart disease.

Right heart catheterization was performed in the Coronary Care Unit using a Swan-Ganz triple lumen catheter inserted from the saphenous vein. Pulmonary arterial and pulmonary capillary wedge pressure were obtained using a strain gauge transducer (Nihonkohden MPU 0.5). Electrocardiographic and pressure recording were made on a direct pen-recorders (Nihonkohden RM 45). Cardiac output (CO) were measured by thermodilution technique using Columbus 108 thermodilution cardiac output computer.^{4),10)} Blood pressure (BP) was obtained with a sphygmomanometer. Pulmonary capillary wedge pressure or pulmonary arterial diastolic pressure was designated as left ventricular filling pressure (LVEP). The following calculation were made.

Mean Blood Pressure (MBP)

$$= \text{Diastolic BP} + \frac{(\text{Systolic BP} - \text{Diastolic BP})}{3} \text{ (mmHg)}$$

Total Peripheral Resistance Index (TPRI)

$$= \frac{\text{MBP} \times 80}{\text{Cardiac Index}} \text{ (dyne} \cdot \text{sec} \cdot \text{cm}^{-5} \cdot \text{M}^2)$$

Stroke Work Index (SWI) = Stroke Index $\times$ (MBP - LVFP) $\times$ 0.0136 (Gm/M²)

Hemodynamic measurements were made before a single injection of chlorpromazine and after 5, 10, 15, 30 min and 1, 2, 3, 4, 5, 6 hours in the treated group. In the control group, hemodynamic measurements were also performed in the same fashion without chlorpromazine.

RESULTS

Percent changes in left ventricular filling pressure and mean blood pressure both in treated group and control group were shown in Figs. 1 and 2. In treated group, a significant reduction of left ventricular filling pressure was observed at 5 min after the injection of chlorpromazine (mean -16.6%,

Fig. 1. Time course of changes in left ventricular filling pressure in 10 patients who were treated with chlorpromazine (Chlorpromazine) and 8 patients without treatment (Control).

Fig. 2. Time course of changes in mean blood pressure in 10 patients who were treated with chlorpromazine (Chlorpromazine) and 8 patients without treatment (Control).

$p < 0.01$). Left ventricular filling pressure showed a peak reduction at 15 min (mean -30.8% , $p < 0.001$) and a significant reduction persisted for 6 hours. Mean blood pressure in treated group showed the time course which was similar to that of left ventricular filling pressure. But the changes were less pronounced and only at 15 min mean blood pressure showed a significant reduction (mean -9.0% , $p < 0.05$). In control group, left ventricular filling pressure and mean blood pressure showed no significant change over 6 hours.

Hemodynamic data before and 15 min after the injection of chlorpromazine were presented in Table I and Figs. 3, 5, 6 and percent changes following the injection were shown in Fig. 4. The left ventricular filling pressure was reduced in all patients from an average of 27.2 ± 1.4 (mean $\pm$ SE) to 18.8 ± 1.6 mmHg ($p < 0.01$), with percent reduction ranging from 6 to 46% (mean -30.8% , $p < 0.001$). In 3 patients who showed severe dyspnea and stridor, the reduction (mean -37%) was greater than in the remaining 7 patients without stridor (mean -28%). Mean blood pressure decreased in 8 patients and rose in 2 patients. The average mean blood pressure was reduced slightly from 101 ± 6 to 92 ± 6 mmHg (mean -9.0% , $p < 0.05$). Heart rate showed no significant change.

Cardiac index increased in 7 patients, unchanged in 2 patients and decreased in 1. The average cardiac index increased slightly, although not

Table I. Hemodynamic Findings Before and 15 Min (Peak Effect)
after Injection of Chlorpromazine

Patient no.	LVFP (mmHg)		MBP (mmHg)		HR (beats/min)		CI (L/min/M ²)		TPRI (dyne·sec· cm ⁻⁵ ·M ²)		SWI (Gm/M ²)	
	before	after	before	after	before	after	before	after	before	after	before	after
1	23	18	78	65	79	78	3.15	3.62	1,396	1,038	29.7	29.6
2	25	16	90	85	89	83	2.11	2.30	2,464	2,400	21.0	26.0
3	23	14	90	78	60	54	2.12	2.22	2,528	2,306	32.2	35.8
4	32	30	98	101	74	68	1.68	1.83	3,142	3,103	20.4	26.0
5	22	16	81	84	63	68	1.85	2.23	2,551	2,439	23.5	30.2
6	34	20	148	128	98	97	2.43	2.46	2,567	2,341	26.2	24.8
7	32	25	98	96	96	97	2.03	1.81	2,600	2,696	18.9	15.4
8	23	18	116	114	108	108	1.44	1.49	5,166	5,154	16.8	17.9
9	32	17	104	92	90	84	2.14	2.74	2,691	2,189	23.2	33.2
10	26	14	104	82	102	101	2.19	2.16	2,849	2,518	22.7	19.7
Mean	27.2	18.8	101	92	85.9	83.8	2.11	2.28	2,795	2,618	23.5	25.9
SE	1.4	1.6	6	6	5.1	5.4	0.14	0.18	298	326	1.5	2.1
p	<0.01		NS		NS		NS		NS		NS	

LVFP=left ventricular filling pressure; MBP=mean blood pressure; HR=heart rate; CI=cardiac index; TPRI=total peripheral resistance index; SWI=stroke work index.

significant, from 2.11 ± 0.14 to 2.28 ± 0.18 L/min/M² (mean +7.8%, NS). The cardiac index was plotted against left ventricular filling pressure and left ventricular function curves were constructed for each of 10 patients (Fig. 5). In all but 1 case, the curves were shifted to the left or to upper left. Stroke work index increased in 6 patients, unchanged in 1 and decreased in 2. The average stroke work index tended to increase slightly from 23.5 ± 1.5 to 25.9 ± 2.1 Gm/M² (mean +10.4%, NS). Total peripheral resistance index

Fig. 3. Changes in left ventricular filling pressure (LVFP), mean blood pressure (MBP), cardiac index (CI) and heart rate (HR) observed 15 min after injection of chlorpromazine. The thick lines indicate the mean changes.

Fig. 4. Percent changes observed 15 min after injection of chlorpromazine. LVFP=left ventricular filling pressure; MBP=mean blood pressure; HR=heart rate; CI=cardiac index; TPRI=total peripheral resistance index; SWI=stroke work index.

Fig. 5. Changes in left ventricular filling pressure and cardiac index observed 15 min after injection of chlorpromazine. Arrows represent the direction of changes after injection of chlorpromazine. The thick arrow indicates the mean change.

tended to reduce slightly from an average of $2,795 \pm 298$ to $2,618 \pm 326$ dyne·sec·cm⁻⁵·M² (mean -9.5%, NS).

Clinical symptoms of pulmonary congestion disappeared or decreased in all patients within 15 min after the injection of chlorpromazine. Particularly, in 3 patients who had severe dyspnea and stridor, the improvement of symptoms was more prominent and rapid. Significant side effects were not observed in any patients. Ventricular premature contractions disappeared in 1 of 5 patients after the injection of chlorpromazine, but frequency of arrhythmia was not increased in any other patients.

Fig. 6. Changes in left ventricular filling pressure and mean blood pressure observed 15 min after injection of chlorpromazine. Arrows represent the direction of changes after injection of chlorpromazine. The thick arrow indicates the mean change.

DISCUSSION

In patients with heart failure, preload reduction by dilatation of the venous system decreases left ventricular filling pressure and pulmonary congestion. Afterload reduction by dilation of arterial system results in an improvement in ejection fraction, a reduction in cardiac work and oxygen demand.^{2),11)} Chlorpromazine has a potent vasodilating effect due to both its effect on the autonomic nervous system and direct action on blood vessels.⁶⁾ In this study, the hemodynamic response to intramuscular injection of chlorpromazine in patients with acute left-sided heart failure showed that elevated left ventricular filling pressure was reduced from an average of 27.2 to 18.8 mmHg (mean -30.8%) at the time of maximal effect. Mean blood pressure was also reduced from an average of 101 to 92 mmHg (mean -9.0%), but percent change was smaller than that in left ventricular filling pressure. From these observations, chlorpromazine appears to show a greater preload reduction than afterload reduction.

Recently, Elkayam and Rotmensh reported the effect of chlorpromazine administered intravenously to patients with acute myocardial infarction and pump failure.¹²⁾ Their observations are in close agreement with our findings, although the way of administration is different. In their report, pulmonary arterial wedge pressure was reduced, as an average, by 38.2% and mean arterial pressure was reduced by 18.3% .

It has been considered that the vasodilator effect of chlorpromazine is, in part, related to its peripheral alpha-blocking action.^{6),7)} However, our study suggests that chlorpromazine appears to exert a greater vasodilator

effect on the venous system than on the arterial system. Therefore, the hemodynamic effect of this drug appears not to be similar to the effect of phenoxybenzamine, an alpha-blocking agent, but may have similarity to the effect of nitroglycerin which shows predominant dilation in the venous system.⁴⁾

The action of chlorpromazine on the left ventricular performance remains unclear. Kido et al demonstrated an inhibitory action of chlorpromazine on the rabbits heart.¹³⁾ In contrast, Gulotta suggested that chlorpromazine increased left ventricular contractility in dogs.⁸⁾ In clinical study, there have been few reports of the direct action on myocardium. But small doses of chlorpromazine may increase cardiac output slightly in patients with shock or heart failure.^{8),9),12)} The study of Loeb et al using intravenous chlorpromazine in an average dose of 11 mg demonstrated an increase in cardiac output in patients with shock.⁹⁾ Similar result was observed in our present study. Cardiac index was slightly increased from an average of 2.11 to 2.28 L/min/M².

There have been few published data on the time course of changes in cardiovascular effects after a single intramuscular injection of chlorpromazine in heart failure. As to sedative effect after a single injection, it has been demonstrated that the effect appears within 30 min and persists 2 to 4 hours.⁶⁾ In the present study, however, left ventricular filling pressure was reduced significantly within 5 min and a peak reduction was observed at 15 min. The significant effect persisted for 6 hours. Symptoms of pulmonary venous congestion such as stridor, dyspnea, or moist rales disappeared also within 15 min and the improvement persisted more than 6 hours. When the hemodynamic effects of chlorpromazine are compared with those of sublingually administered nitroglycerin or isosorbide dinitrate, the former exerts more rapid and longer effect than the latter.^{3),4),14)}

Another beneficial effect of chlorpromazine is a sedative effect. In the presence of severe dyspnea due to acute pulmonary edema, patients react to it with pronounced anxiety and distress which increase the work of heart and oxygen demand.⁵⁾ Anxiety also increases respiratory rate with resultant augmentation of the work of the respiratory muscles. They may be reduced by the sedative effect of chlorpromazine. It has been assumed that chlorpromazine depresses the respiratory center by its effect on the brain stem.⁶⁾ This effect may decrease hyperventilation and dyspnea. But, following a single intramuscular injection of small dose of chlorpromazine, the decrease in respiratory minute or tidal volumes has been reported to be minimal,¹⁵⁾ and no significant changes of arterial PO₂ and PCO₂ were found in 4 patients in this study.

In vasodilation therapy, a fall in blood pressure is of advantage to reduce afterload, but it may be of disadvantage to reduce perfusion pressure in the organs. Especially, in patients with acute myocardial infarction, whose coronary blood flow may be mainly dependent on the perfusion pressure because of severe coronary narrowing, perfusion pressure of the coronary artery is considered to be of great importance. The risk of hypotension after administration of chlorpromazine⁷⁾ has been pointed out. However, in the present study, the fall of blood pressure was slight and there was no patient who showed symptomatic hypotension or clinical deterioration even in those with acute myocardial infarction. For long term vasodilation therapy, short-acting agents such as phentolamine or sodium nitroprusside should be administered by drip infusion under careful and frequent monitoring of blood pressure because of the risk of profound hypotension. In contrast, the sustained action of chlorpromazine can eliminate the need for drip infusion and requiring less frequent administration. Further studies would be required to evaluate the effect of long term therapy by this agent, including oral administration of the agents in patients with chronic congestive heart failure.

REFERENCES

1. Majid PA, Sharma B, Taylor SH: Phentolamine for vasodilator treatment of severe heart failure. *Lancet* **2**: 719, 1971
2. Guiha NH, Cohn JN, Mikulic E, Franciosa J, Limus CJ: Treatment of refractory heart failure with infusion of nitroprusside. *N Engl J Med* **291**: 587, 1974
3. Franciosa JA, Mikulic E, Cohn JN, Jose E, Fabie A: Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure. *Circulation* **50**: 1020, 1974
4. Mifune J, Kuramoto K, Ueda K, Matsushita S, Kuwajima I, Sakai M, Ikehata K, Kitano K, Murakami M: Vasodilation therapy in congestive heart failure—hemodynamic effects of isosorbide dinitrate and nitroglycerin. *Shinzo* **8**: 1427, 1976 (in Japanese)
5. Goldberg LI: Pharmacology of cardiovascular drugs. in *The Heart*, ed by Hurst JW, 3rd ed, McGraw—Hill, NY, P 1559, 1970
6. Byck R: Drugs and the treatment of psychiatric disorders. in *The Pharmacological Basis of Therapeutics*, ed by Goodman LS, Gilman A, 5th ed, Macmillan, NY, P 152, 1975
7. Stimmel B: The effects of mood altering drugs on the heart. in *Drugs in Cardiology*, Vol 1, Part 1, ed by Donoso E, 1st ed, Grune & Stratton, NY, p 203, 1975
8. Gulotta SJ: Chlorpromazine in the treatment of cardiogenic shock. *Am Heart J* **80**: 570, 1970
9. Loeb HS, Pietras RJ, Ninos N, Tobin J, Gunnar RM: Hemodynamic responses to chlorpromazine in patients in shock. *Arch Intern Med* **124**: 354, 1969
10. Ganz W, Swan HJC: Measurement of blood flow by thermodilution. *Am J Cardiol* **29**: 241, 1972
11. Mason DT: Regulation of cardiac performance in clinical heart disease. in *Congestive Heart Failure*, ed by Mason DT, 1st ed, Grune & Stratton, NY, P 111, 1976
12. Elkayam U, Rotmensch HH: Hemodynamic effects of chlorpromazine in patients with acute myocardial infarction and pump failure. *Chest* **72**: 623, 1977

13. Kido R, Hirose K, Yamamoto K, Hiraoka K: Pharmacology of chlorpromazine. Ann Rept Shionogi Res Lab **6**: 171, 1956 (in Japanese)
14. Mifune J, Kuramoto K, Ueda K, Matsushita S, Kuwajima I, Sakai M, Iwasaki T, Inoue H, Shinagawa T, Murakami M: Hemodynamic comparisons between oral and sublingual isosorbide dinitrate in heart failure (abstr). Jap Circulat J **41**: 786, 1977
15. Dobkin AB, Gilbert RGB, Lamoureu L: Physiological effects of chlorpromazine. Anaesthesia **9**: 157, 1954