Phentolamine : Use in Pulmonary Edema

Preliminary Report

Lawrence GOULD, M.D.,* Mohammad ZAHIR, M.D.,** Mahmood SHARIFF, M.D.,** and Marguerite GIULIANI, M.D.**

SUMMARY

In 6 patients with pulmonary edema, the intravenous administration of phentolamine at a rate of 0.3 mg./min. resulted in a rapid alleviation of symptoms and signs.

In one patient with severe left ventricular failure a complete hemodynamic study was possible and the infusion of phentolamine produced a striking improvement in the measured hemodynamic functions.

Phentolamine may prove to be a valuable and effective drug for the treatment of patients in pulmonary edema due to left ventricular failure.

Additional Indexing Words:

Congestive heart failure Inotropic drug

TAYLOR and his co-workers¹⁾⁻³⁾ have investigated the hemodynamic effects in man of the acute intravenous injection of 5 mg. of phentolamine and of the intravenous infusion of phentolamine at a rate of 2 mg./min. for 10 min. Both methods of administration produced an increase in the heart rate and cardiac output and a decrease in the systemic arterial pressure and systemic vascular resistance. They postulated that the decrease in the peripheral resistance produced a reflex increase in the cardiac output. Evans, Smulyan, and Eich⁴⁾ made a similar observation and came to a similar conclusion. Measurements of the force of contraction using a strain gauge arch, or of the speed of contraction employing the left ventricular dp/dt , were not, however, utilized by these workers. On the other hand, Goodman and Gilman⁵⁾ state that phentolamine given intravenously produces vasodilatation and cardiac stimulation and that blood pressure response depends upon the relative contribution of these two effects. The vasodilatation is due primarily to a direct action on vascular smooth muscle, although, with higher doses, alpha adrenergic blockade may also be involved.

Recent work in our laboratory⁶⁾ has lent support to the observations of

From the Medical Service of the Veterans Administration Hospital, Bronx, New York 10468.

* Chief, Cardiology Section

** Chief Resident, Cardiology Section

Received for publication September 1, 1969.

Goodman, and Gilman. We administered 5 mg. of phentolamine intravenously to 4 normal mongrel dogs, each with a strain gauge arch attached on the right ventricle. After the administration of the drug, an average increase of 102 % was observed in the ventricular contractile force. Phentolamine was then given by intravenous drip for 20 min. at a rate of 0.3 mg./min. to 5 patients with relatively normal left ventricles, who had never been in left ventricular failure, and to 13 patients with abnormal left ventricles, who had previously been in left ventricular failure. In the patients with relatively normal left ventricles, the administration of phentolamine produced little or no change in the heart rate, cardiac pressures, cardiac output or left ventricular volume. Since these hemodynamic parameters remained essentially unchanged, the observed 58 % average increase in the left ventricular first derivative could be attributed to an increase in ventricular contractility. In the patients with abnormal left ventricles, phentolamine administration produced an increase in the cardiac output, systemic pressure, cardiac rate and left ventricular dp/dt and a fall in the pulmonary artery pressure, systemic peripheral resistance, left ventricular end-diastolic pressure and left ventricular end-diastolic volume. It is clear, therefore, that phentolamine does indeed have a dual action. It is a positive inotropic agent and it reduces the systemic peripheral resistance, particularly in patients in congestive heart failure.

If these favorable hemodynamic effects could be produced in patients with pulmonary edema, then this drug would be a valuable addition to the physician's armamentarium. We have, therefore, administered phentolamine to 6 patients in pulmonary edema, and to 1 patient in very severe left ventricular failure. The results confirm the potency of the drug's action and its effectiveness in producing rapid alleviation in this cardiovascular emergency.

METHODS

Six patients with spontaneous pulmonary edema were treated with an intravenous infusion of phentolamine. This was accomplished by placing 3 ampules or 15 mg. of phentolamine in 200 ml. of glucose and water. The resultant mixture was infused at a rate of 60 drops (0.3 mg.) per min. into the antecubital vein. Rotating tourniquets were not used during the infusion of the drug, and no patient was treated with additional digitalis or morphine at the time of the infusion.

Serial blood pressure recordings and electrocardiograms were obtained prior and subsequent to the drug administration. Auscultation of the lungs was frequently performed to observe any objective clinical improvement. The phentolamine infusion was discontinued when a marked improvement in the clinical status of the patient was observed.

Table I. Patients in Pulmonary Edema

Phentolamine Infusion												
Case No. 1	Control	5 min.	8 min.	10 min.	13 min.	17 min.	21 min.	26 min.	30 min.	34 min.	38 min.	40 min.
Blood Pressure	170 110	150 94	160 94	160 92	160 90	160 94	160 92	154 88	152 90	148 90	150 84	150 82
Cardiac Rate	100	95	95	95	95	95	95	95	95	95	95	95
Resp. Rate	36											20
Phentolamine												
Case No. 2	Control	5 min.	10 min.	15 min.	20 min.							
Blood Pressure	230 110	220 100	224 96	226 90	190 90							
Cardiac Rate	110	120	120	120	120							
Resp. Rate	36				18							
Phentolamine												
Case No. 3	Control	20 min.	35 min.	50 min.	65 min.							
Blood Pressure	180 96	160 90	150 95	140 80	125 90							
Cardiac Rate	96	90	95	96	100							
Resp. Rate	28				18							
Case No. 4	Control	5 min.	7 min.	9 min.	11 min.	13 min.						
Brachial Artery Pressure (mm.Hg)	130 20	120 30	120 28	120 28	120 25	110 28						
Resp. Rate	36					18						
Phentolamine												
Case No. 5	Control	1 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.				
Blood Pressure	250 160	240 150	238 140	240 144	240 138	240 138	240 134	240 130				
Cardiac Rate	130	130	130	130	130	130	130	130				
Resp. Rate	38							20				
Phentolamine												
Case No. 6	Control	4 min.	8 min.	12 min.	16 min.	20 min.	24 min.	28 min.				
Blood Pressure	110 80	100 80	100 80	90 70	90 70	96 70	92 70	98 70				
Cardiac Rate (Atrial fibrillation)	165	165	160	160	140	160	150	150				
Resp. Rate	32							20				

CASE REPORTS

Case 1. A 52-year-old negro male with primary myocardial disease was admitted to the hospital because of rapidly increasing dyspnea over a period of several days despite previous digitalis maintenance therapy. When seen, he was in acute distress with marked dyspnea, cyanosis, jugular venous distension, diastolic gallop, hepatomegaly of 7 cm. and signs of pulmonary edema. An electrocardiogram was compatible with left ventricular and left atrial hypertrophy.

Rotating tourniquets were applied, and 2 ml. of Mercuhydrin was given intramuscularly. Fifty min. later no clinical improvement was observed and phen-tolamine was then administered intravenously at a rate of 0.3 mg./min. for 40 min. Serial blood pressure recordings and electrocardiograms were obtained. A fall in the blood pressure occurred within 5 min., and by the end of the infusion the patient was virtually asymptomatic. Only a few basilar rales persisted. No arrhythmias were noted during the study (Table I).

Case 2. A 65-year-old white male with diabetes, hypertension and arterio-sclerotic heart disease was being treated for Bell's palsy. While in the hospital, he developed the signs and symptoms of pulmonary edema. An electrocardiogram revealed an acute anterior wall myocardial infarction and occasional ventricular premature contractions. Phentolamine was administered at a rate of 0.3 mg./min. for 20 min. Serial blood pressures and electrocardiograms were obtained. A rapid fall in the blood pressure occurred and by the end of the infusion the patient was markedly improved (Table I).

Case 3. A 78-year-old white male with diabetes mellitus and arteriosclerotic heart disease was admitted to the hospital in acute pulmonary edema. An electrocardiogram revealed sinus tachycardia and occasional ventricular premature

Table

	Phentolamine Infusion							
	Control	2 min.	3 min.	5 min.	10 min.	15 min.	20 min.	30 min.
Brachial Artery Pressure (mm.Hg)	165 110	170 110	165 105	170 105		170 100		170 100
Left Ventricular Pressure (mm.Hg)	155 32			165 15	160 17		150 17	155 18
Pulmonary Artery Pressure (mm.Hg)	85 42				75 40		75 40	75 40
Pulse Rate (beats/min.)	115	120	120	120	120	115	107	107
Cardiac Index (L./min./M. ²)	2.73						5.15	
Stroke Index (ml./beat/M. ²)	24						45	
Arteriovenous Oxygen Difference (Vol. %)	7.0						4.5	
Oxygen Consumption (ml./min./M. ²)	190						232	

contractions. Phentolamine was administered at a rate of 0.3 mg./min. for 65 min. and serial blood pressures and electrocardiograms were obtained. A marked improvement in the clinical status occurred in 20 min. and by the end of the infusion the patient was asymptomatic and the lungs were free of rales (Table I).

Case 4. A 54-year-old white male with known aortic valve disease was admitted to the hospital with chills and fever of 2 weeks duration. The physical examination revealed aortic insufficiency, and the diagnosis of bacterial endocarditis was confirmed when *Streptococcus viridans* grew out in blood cultures. The fever rapidly subsided with the administration of penicillin and streptomycin. Subsequently 2 bouts of pulmonary edema occurred and were successfully treated by using rotating tourniquets and morphine. A third episode of pulmonary edema occurred which did not respond to the application of rotating tourniquets. Fifty mg. of ethacrinic acid was then given intravenously, but after $2\frac{1}{2}$ hours no diuresis ensued, and the patient was deteriorating clinically. A Cournand needle was inserted into the brachial artery in order to obtain arterial pressures, utilizing a Satham pressure transducer—P23Db and the Electronics for Medicine Recorder. Phentolamine was administered at a rate of 0.3 mg./min. for 13 min. A slight fall in the arterial systolic pressure was observed (Table I). By the end of the infusion a marked clinical improvement resulted, with clearing of the pulmonary rales, with a diuresis of 200 ml. (Table I).

Case 5. A 49-year-old negro male with a previous history of hypertension and diabetes mellitus was admitted to the hospital in pulmonary edema. He had previously been on digitalis and diuretic therapy. Rotating tourniquets and morphine were successful in relieving the pulmonary edema. Two days after the admission, another episode of pulmonary edema occurred. Phentolamine was now administered at a rate of 0.3 mg./min. for 30 min. Serial blood pressures and electrocardiograms were obtained. A rapid fall in the blood pressure occurred and by the end

II

40 min.	45 min.	60 min.	Infusion Stopped							
			2 min.	3 min.	4 min.	5 min.	10 min.	20 min.	25 min.	30 min.
	150 85	145 80	150 85	150 85	145 85	150 85	150 85	145 85		
150 17		140 15					140 17	140 15		140 17
	65 35	55 95					55 25	55 25		
107	100	95	95	95	95	95	95	95	100	95
		4.34							4.14	
		46							42	
		5.0							4.7	
		217							195	

of the infusion a marked clinical improvement was observed (Table I).

Case 6. A 68-year-old white male with no antecedent history of heart disease was admitted to the hospital because of cough of one month's duration. Shortly after admission, signs and symptoms of pulmonary edema developed. An electrocardiogram showed atrial fibrillation with a rapid ventricular response averaging 165 per min. A phentolamine infusion was started without recourse to other modes of therapy. At the conclusion of the infusion, a marked clinical improvement was observed (Table I).

Case 7. A 46-year-old negro male with cardiac disease of unknown etiology was admitted to the hospital in congestive heart failure. Basal rales and a pre-systolic and protodiastolic gallop were present. An electrocardiogram revealed left ventricular hypertrophy. In spite of digitalis and diuretic administration there was only minimal clinical improvement. The patient underwent right and left heart catheterization to rule out the presence of a surgically correctable lesion. Catheterization of the left ventricle was performed by the Seldinger technique. A Cournand needle was placed into the brachial artery, and a number 7 Goodale-Lubin catheter was placed in the pulmonary artery. Cardiac output was determined by the Fick method. Left ventricular, pulmonary arterial and systemic arterial pressures and cardiac output were measured in the control state. No valvular abnormalities were demonstrated, and primary myocardial disease was considered to be the most likely diagnosis. Phentolamine was then given by constant intravenous drip (0.3 mg./min.). Pressure recordings and cardiac output values were determined during the one hour infusion, and 30 min. after the cessation of the drug (Table II).

The control mean pulmonary artery wedge pressure was 35 mm.Hg, the left ventricular pressure was 155/32 and the pulmonary artery pressure was 85/42. During the first few min. of the infusion the left ventricular and brachial arterial systolic pressures rose, while the pulmonary artery pressure fell. By the end of the infusion the brachial artery, left ventricular and pulmonary artery pressure declined and approached normal values. A striking rise in the cardiac output with a narrowing of the arteriovenous oxygen difference were also observed. These beneficial hemodynamic effects persisted for 30 min. after the cessation of phentolamine infusion. A commensurate improvement in the clinical status of the patient was observed.

DISCUSSION

Taylor and his workers²¹ observed a prompt reduction in the pulmonary arterial and systemic arterial pressure and an increase in the cardiac output, after the acute intravenous injection of 5 mg. of phentolamine. They postulated that this drug, due to its direct vasodilator properties could be of benefit in treating patients with pulmonary edema, but they did not report its clinical use. Our demonstration of the positive inotropic action of this drug and of the marked improvement of cardiac dynamics in patients in congestive heart failure suggested that this agent could improve patients in very severe left ventricular failure and pulmonary edema.

Improvement was observed in our 7 patients after phentolamine adminis-

tration. The blood pressure is usually elevated in patients with pulmonary edema unless they are in shock. With successful treatment, the blood pressure will fall to the pre-pulmonary edema values. All of our patients in pulmonary edema demonstrated, with phentolamine administration, a rapid decrease in the arterial pressure and prompt clinical improvement. This was presumably associated with a fall in the pulmonary artery pressure and an increase in cardiac output. No arrhythmias or untoward effects occurred during the infusion of the drug.

A reduction in the peripheral resistance, with decreased systolic load on the heart, undoubtedly played a role in the relief of pulmonary edema. Left ventricular contractility was not measured in these patients, but our earlier observations indicate that a positive inotropic action also played an important role.⁶⁾ The positive inotropic action of phentolamine may be due to a direct or an indirect mechanism. (1) Phentolamine may act as isoproterenol and directly stimulate the beta adrenergic receptor sites in the heart; (2) phentolamine may act as morphine and produce a sympatho-adrenal discharge which indirectly stimulates the beta adrenergic receptors of the myocardium.⁷⁾ Recently, Dairman and his associates⁸⁾ have presented data which throws new light on phentolamine's mechanism of action. They administered the drug (5 mg./Kg.) to rats. At the height of receptor blockade, the conversion of a tracer dose of tyrosine-C¹⁴ to norepinephrine in heart, brain and adrenals was increased threefold with no alteration in specific activity of tyrosine in blood and tissues. From these studies, Dairman concluded that receptor blockade led to increased synthesis and release of norepinephrine in the 3 organs in which measurements were made. Our studies with smaller doses of phentolamine, have indicated a positive inotropic effect, and in view of Dairman's findings, it could be reasonably assumed that this inotropic effect is a direct one, resulting from increased production of catecholamines in the myocardium.

It appears, therefore, that phentolamine is highly effective in the treatment of patients in pulmonary edema due to left ventricular failure. In this small series of cases it was effective, rapid in action, and devoid of side effects including arrhythmias. These favorable results warrants further investigation of this drug in the treatment of pulmonary edema.

REFERENCES

1. Taylor, S. H., Sutherland, G. R., Mackenzie, G. J., Staunton, H. P., and Donald, K. W.: *Circulation* **31**: 741, 1965.
2. Taylor, S. H., Mackenzie, G. J., and McDonald, A.: *Brit. Heart J.* **27**: 627, 1965.
3. Taylor, S. H., Sutherland, G. R., Mackenzie, G. J., Staunton, H. P., and Donald, K. W.: *Clin. Sci.* **28**: 265, 1965.

4. Evans, G. L., Smulyan, H., and Eich, R. H.: *Am. J. Cardiol.* **20**: 216, 1967.
5. Goodman, L. S. and Gilman, A.: *The Pharmacological Basis of Therapeutics*, 3rd ed., Macmillan Company, New York and London, p. 557, 1965.
6. Gould, L., Zahir, M., and Ettinger, S.: *Brit. Heart J.* **31**: 154, 1969.
7. Vassale, M.: *Am. J. Physiol.* **200**: 530, 1961.
8. Dairman, W., Gordon, R., Spector, S., Sjoerdsma, A., and Udenfriend, S.: *Fed. Proc.* **27**: 240, 1968.