THE ACUTE HEMODYNAMIC EFFECTS OF ORAL IBOPAMINE IN PATIENTS WITH CONGESTIVE HEART FAILURE

C. ÇELİKER, M.D.
R. ENAR, M.D.
N. YAZICIOĞLU, M.D.
C. DEMİROĞLU, M.D.

The acute hemodynamic effects of 100 mg ibopamine, an orally active dopaminergic agent, were assessed invasively in 100 patients with congestive heart failure (CHF). Hemodynamic measurements were obtained using a Swan-Ganz thermodilution catheter and cardiac output computer.

The hemodynamic effects occured as early as 30 minutes and lasted up to 4 hours after administration of the drug. Ibopamine did not induce any significant change in arterial pressure and heart rate. Cardiac index increased significantly ($p<0.05$) from 1.95 to 2.82 $L/min/m^2$. A biphasic response in pulmonary capillary wedge pressure (PCWP) was observed, up to 1 hour after administration. Ibopamine elevated PCWP from 20.4 to 25.6 mmHg ($p<0.025$) with significant reduction to 16.6 mmHg ($p<0.005$) at the third hour.

In conclusion, oral ibopamine elicits favorable hemodynamic effects in patients with CHF, however more extensive studies after chronic treatment are needed.

From: University of İstanbul, Institute of Cardiology

Adress for reprints:
C. Çeliker, MD,
University of İstanbul,
Institute of Cardiology
Haseki, İstanbul, Türkiye

Key words: Congestive heart failure, ibopamine

The main drugs that are used in the medical treatment of chronic congestive heart failure (CHF) are inotropic, diüretic, and vasodilator agents. It is now well known that the indication for digitalis glycosides are limited in contrary to the growing importance of inotropic sympathomimetic amines. In this group of drugs, dopamine and dobutamine are effective intravenously in short term therapy. Ibopamine is a new, orally active dopamine derivative (di-isobutyric ester of N-methyldopamine) with a predominant action on dopaminergic and ß receptors resulting in cardiac stimulation and vasodilation[1].

We have undertaken the present study to evaluate the acute hemodynamic effects of 100 mg ibopamine in patients with CHF.

Materials and Methods

The study group included 10 patients (8 male) aged 49±9 years (range 38-64 yrs) with severe CHF. The etiology of heart failure consisted of idiopathic dilated cardiomyopathy in 9, and coronary artery disease in 1 patient. The diagnosis was established on the basis of clinical findings, chest roentgenogram, echocardiogram, cardiac catheterization, and left ventricular and coronary angiography. The left ventricular ejection fraction was <0.30 in all of the patients. They were all in New York Heart Association (NHYA) class IV, refractory to conventional treatment with digoxin, diuretics, and vasodilators. Vasodilator drugs were discontinued 3 days, digoxin and diuretics 1 day before the study.

The patients were admitted to the coronary care unit before the study. A flow-directed, triple-lumen thermodilution Swan-Ganz catheter (Spectramed model SP 5107H) was inserted percutaneously into a subclavian vein. After a 30 minute rest period, baseline hemodynamic measurements were obtained until two successive values varied by less than 10%. Measured hemodynamic variables included mean pulmonary artery pressure (PAP), mean right atrial pressure (RAP), and pulmonary capillary wedge pressure (PCWP). Systolic and diastolic arterial blood pressures (SAP and DAP) were determined by cuff sphygmomanometry. Mean arterial pressure (MAP) was calculated according to the formula: MAP = (2DAP + SAP) /3. Heart rate (HR) was recorded from a continuously monitored electrocardiogram. Cardiac index (CI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were measured by thermodilution with Spectramed Hemopro 1 cardiac output computer. After a single oral dose of 100 mg of ibopamine was given, hemodynamic measurements were performed at 30 minutes and 1, 2, 3, 4, 6, 8 and 24 hours.

All values were expressed as mean ± standard deviation. Statistical analysis was performed using student's t test, and the changes with $p<0.05$ was considered statistically significant.

Results

The values of HR, MAP, RAP, PAP, PCWP, CI, SVR, and PVR before and after oral administration of 100 mg ibopamine are shown in Table I.

Prior to treatment, the mean PAP, PCWP, SVR, and PVR values were high and CI was low. HR and MAP did not change significantly after ibopamine administration. RAP increased form 4.4±4.6 mmHg to 7.6 ± 6.8 mmHg 1 hour after ibopamine administration, but the change was not significant (Figure 1). PAP also increased insignificantly up to 1 hour after ibopamine administration and reduced to its initial values at 2 hours (Figure 1). PCWP rose significantly ($p<0.025$, $p<0.05$) by 25.5% to 25.6±5.6 mmHg and 24±4.6 mmHg at 30 minutes and 1 hour after ibopamine administration, respectively (Figure 1). PCWP decreased significantly ($p<0.005$) by 18.6% to 16.6±1.5 mmHg at 3 hours after ibopamine administration. CI began to increase at 30 minutes, but increased significantly ($p<0.05$) by 44.6% after 1 hour up to 4 hours (Figure 2). The values of SVR and PVR (except at 6 hours) decreased, but the change was not significant.

One patient complained of nausea, but no toxic side effects were observed.

Discussion

In patients with severe CHF refractory to the conventional medical treatment, the primary requirement is to improve cardiac contractility. New orally used inodilator drugs have recently been introduced for this purpose. Among this group of agents, the acute hemodynamic effects of 100 mg ibopamine in patients with CHF has been studied.

The main favorable hemodynamic effect of ibopamine that we detected was significant increase of CI up to 45%, begining at 30 minutes after ibopamine administration lasting 4 hours. We did not see any significant changes in HR and MAP durig this period. In short-term studies[2-6, 8-11] with single-dose (50-300 mg) ibopamine, CI increased about

Table I. Hemodynamic parameters before and after ibopamine treatment

	Before	30 min	1 h	2 h	3 h	4 h	6 h	8 h	24 h
Heart rate (beats/min)	108±13.5	109±10.2	110.2±15.5	109±18.4	110.8±15.9	111.6±14.9	108.2±14.9	112±13.6	110.4±17.2
MAP (mmHg)	101.9±8.4	99.6±4.8	99.3±8.03	98.3±5.5	101.6±6.9	102.6±3	101.9±10.5	101±7.4	95.7±8.8
RAP (mmHg)	4.4±4.6	4.4±6.7	7.6±6.8	4.8±4.6	4.4±3.4	5±6.4	6.4±6.7	7.6±6.6	6.4±5.4
PAP (mmHg)	30.6±6.9	34.8±7.4	34.6±8.6	31.8±5.5	28±6.8	29.6±6.1	30±3.4	31.2±7.1	33.8±6.5
PCWP (mmHg)	20.4±2.2	25.6±5.6**	24±4.6*	20±5.2	16.6±1.5***	22.2±9.1	25.6±7.7*	23.8±6.8	24±10.1
CI (L/min/m^2)	1.95±0.7	2.32±0.5	2.56±0.7*	2.82±0.81*	2.8±0.85*	2.8±0.93*	2.4±0.7	2.3±0.7	2.14±0.7
SVR (dyn. sec. cm-5)	3228±1611	2512±934	2246±1079	2155±2106	2245±1328	2416±1665	2574±1387	2530±1159	2709±1525
PVR (dyn. sec. cm-5)	381±359	261±181	333±360	289±273	298±324	168±123	101±98*	268±319	318±362

Values: Mean± Standart deviation, h:hour, MAP: mean arterial pressure, RAP:right atrial pressure, PAP: pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac index, SVR: systemic vascular resistance, PVR: pulmonary vascular resistance.
*: $p<0.05$, **: $p<0.025$, ***: $p<0.005$

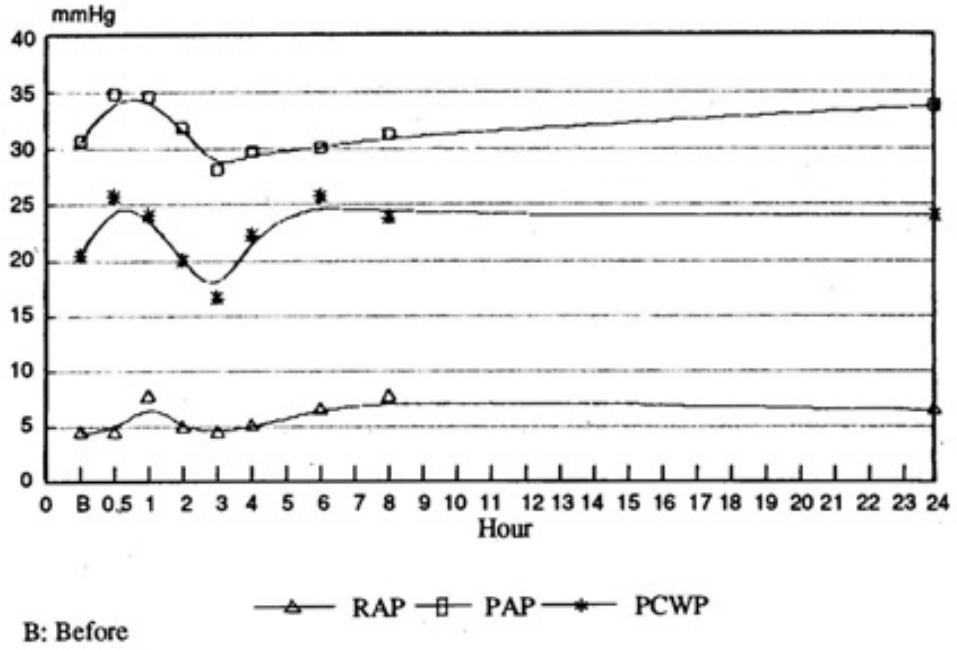

Figure 1. The values of right atrial (RAP), pulmonary artery (PAP), and pulmonary capillary wedge pressures (PCWP) before and after ibopamine treatment.

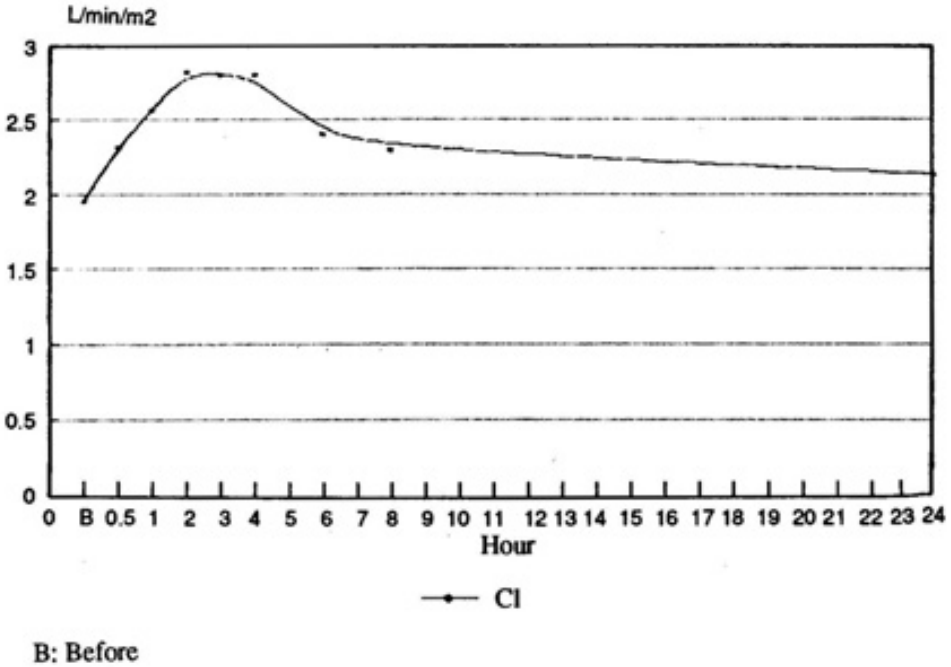

Figure 2. The value of Cardiac Index (CI) before and after ibopamine treatment.

10-44%. Lopez-Sendon[7] who collected the results of 28 studies about the acute hemodynamic effects of single-dose of ibopamine reported a small but significant increase in blood pressure in only 3, and an increase in HR in 4 studies. In other studies [2-6,8,10,11] no significant change was reported.

The second important finding of the present study was the significant increase in PCWP during the first 30 minutes, and 1 hour after ibopamine administration, and 18% significant reduction at 3 hours. Lopez-Sendon[7] reported a small but statistically significant increase in RAP or PCWP during the first 15-60 minutes, and 10-17% significant reduction after 1-2 hours in 9 of 28 studies. In other studies[3,10,11] RAP or PCWP decreased about 30% without any transient increase. This biphasic hemodynamic response could be explained by the increase in venous pressure secondary to α-mediated venous constriction or the relatively higher increase in CI in relation to the small decrease in PVR observed shortly after drug ingestion. It was reported[7,9] that this early increase in PCWP was associated with dyspnea in 8 of 325 patients. In our study, only one patient complained about a mild dyspnea that continued shortly.

We found insignificant reduction in SVR and PVR. It was reported[2-7,10,11] 10-29% decrease in SVR, and 17-29% reduction in PVR reflecting the vasodilating effect of ibopamine.

Dose-dependent increase in hemodynamic effects of ibopamine was reported in some series[2,7,10]. It is accepted that the beneficial effects of ibopamine begin 30 minutes after ibopamine administration, reaching at peak effect at 1-2 hours, lasting in 4 to 8 hours[7,8,10]. Dei Cas et al[5] reported that high doses (100 mg 8 times a day) of ibopamine in patients with severe refractory heart failure could favorably substitute for the intravenous infusion of dopamine and keep patients hemodynamically stable without any evidence of tolerance development.

In conclusion, our results show that acute oral administration of ibopamine elicits favorable inotropic and vasodilatory hemodynamic effects in patients with CHF for 4 hours. It would be better to talk about its chronic efficacy after the results of more extensive long-term studies are published, and its lack of development of tolerance is understood. We think that it would be useful to add oral ibopamine to treatment protocol of patients refractory to traditional treatment (digoxin, diuretic, vasodilators) of CHF.

References

1- Holubarsch C, Just H: The safety profile of ibopamine, an alternative substance for treatment of chronic heart failure. Cardiology 1990; 77 (suppl 5):1-8.

2- Leier CV, Ren JH, Huss P, Magorten RD, Unverferth DV: Ibopamine in congestive heart failure. Circulation 1983; 68 (III):373-380.

3- Col J, Mievis E, Reynaert M: Ibopamine in very severe congestive heart failure. Pilot hemodynamic invasive assessment. Eur J Clin Pharmacol 1983; 24:297-300.

4- Leier CV, Ren JH, Huss P, Unverferth DV: The hemodynamic effects of ibopamine, a dopamine congener, in patients with congestive heart failure. Pharmacotherapy 1986; 6:35-40.

5- Dei Cas L, Metra M, Nodari S, Visioli O: Efficacy of ibopamine treatment in patients with advanced heart failure: Purpose of a new therapeutic scheme with multiple daily administrations. J Cardiovasc Pharmacol 1989; (suppl 8):111-117.

6- Dei Cas L, Fappani A, Riva S, et al: Hemodynamic advantage of combined administration of ibopamine and nitroprusside in patients with ischemic and idiopathic congestive cardiomyopathy. Clin Cardiol 1985; 8:427-432.

7- Lopez-Sendon J: Hemodynamic and neurohumoral effects of ibopamine in patients with chronic congestive heart failure. Cardiology 1990; 77 (suppl 5): 9-21.

8- Ren JH, Unverferth DV, Leier CV: The dopamine congener ibopamine, in congestive heart failure. J Cardiovasc Pharmacol 1984; 6:748-755.

9- Hogg KJ, Hournung RS, Howie CA, Hillis WS: Early cardiovascular changes with ibopamine. Evidence for a biphasic

hemodynamic action. Br J Clin Pharmacol 1987; 24:435-442.

10- Rajfer SI, Rossen JD, Douglas FL, Goldberg LI, Karrison T: Effects of long term therapy with oral ibopamine on resting and exercise capacity in patients with heart failure. Relationship to the generation of N-methyldopamine and to plazma norepinephrine levels. Circulation 1986; 73:740-748.

11- Dei Cas L, Bolognesi R, Cucchini F, Fappani A, Riva S, Visioli O: Hemodynamic effect of ibopamine in patients with idiopathic congestive cardiomyopathy. J Cardiovasc Pharmacol 1983; 5:249-253.