Effects of Intravenous Amrinone on Heart Failure Complicated by Acute Myocardial Infarction: Comparative Study with Dopamine and Dobutamine

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The hemodynamic effects of a newly developed inotropic agent, amrinone (AMN) were studied and compared with those of dopamine (DA) and dobutamine (DB) in forty patients with pump failure due to acute myocardial infarction. Hemodynamic measurements were taken using a Swan-Ganz thermodilution catheter before and 5, 10, 15, 30, 60, 90 and 120 minutes after intravenous injection of AMN (1–2 mg/kg) for 3 minutes in eight patients, and also before and during drip infusion (3–7 μ g/kg/min) of DA in fifteen patients and DB in seventeen patients.

AMN showed maximal increases in CI, SVI and SWI, and maximal lowering in CVP and SVR 5 minutes after intravenous injection, while maximal lowering in PCWP occurred 10 minutes after injection. These significant hemodynamic changes lasted for 60 minutes after injection. Comparing the maximal hemodynamic effects occurring 5 minutes after injection of AMN with those of DA and DB, it was found that AMN increased CI to almost the same degree as DA, and lowered CVP and PCWP much more compared to DB. These results suggest that AMN possesses a dominant vasodilating effect in addition to its inotropic effect, which would greatly benefit the treatment of refractory heart failure; AMN are the characteristic cardiovascular hemodynamic effects of as if catecholamine and a vasodilator were combined.

AMRINONE (5-amino-3,4'-bipyridine-6(1H)-one), one of the bipyridine derivatives, is a new inotropic agent first introduced by Farah and Alousi.¹ Its precise mechanism of action is unknown but it is unrelated to the mechanisms of inotropic action of digitalis or catecholamine. Recent work has suggested that a possible positive inotropic effect of amrinone is that it increases the concentration of intracellular cyclic AMP by inhibition of phosphodiesterase (PDE).

Because amrinone's mechanism of action is different from that of other inotropic agents and

so is assumed to have a different effect on hemodynamics, we administered amrinone intravenously to patients with heart failure due to acute myocardial infarction to investigate its hemodynamic effect, and to compare the effect with those of dopamine and dobutamine, the drugs most frequently used at present as catecholamine preparations.

PATIENTS AND METHODS

Forty patients with acute myocardial infarction complicated by heart failure showing pulmonary capillary wedge pressure of 18 mmHg or above were studied in the coronary care unit of Nippon Medical School.

Key Words:

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TABLE I HEMODYNAMIC RESPONSES TO INTRAVENOUS INJECTION OF AMRINONE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION (n = 8)

	Control	5 min	10 min	15 min	30 min	60 min	90 min	120 min
HR (beat/min)	88 ± 14	94 ± 18	94 ± 15*	92 ± 15	91 ± 15	90 ± 15	89 ± 15	91 ± 14
BPm (mmHg)	89 ± 19	87 ± 22	84 ± 16	87 ± 17	85 ± 17	85 ± 16	85 ± 12	88 ± 17
CI (L/min/M ²)	2.03 ± 0.38	2.57 ± 0.43***	2.32 ± 0.38*	2.28 ± 0.31*	2.42 ± 0.50**	2.25 ± 0.34*	2.26 ± 0.46	2.20 ± 0.43
SVI (ml/beat/M ²)	23.5 ± 5.1	27.9 ± 5.8*	25.1 ± 5.5	25.4 ± 4.8	27.3 ± 7.4	25.6 ± 4.8	25.7 ± 5.8	24.7 ± 5.8
SWI (gm-M/beat/M ²)	39.1 ± 17.2	48.0 ± 19.8*	41.7 ± 13.2	44.3 ± 17.5	46.5 ± 21.1	44.3 ± 17.6	42.0 ± 15.6	42.4 ± 17.4
CVP (cmH ₂ O)	9.5 ± 4.6	6.0 ± 3.0**	6.5 ± 3.0**	6.9 ± 3.9**	7.2 ± 3.5**	7.2 ± 4.3**	8.0 ± 4.4	8.1 ± 3.4
PCWP (mmHg)	23.0 ± 2.7	17.9 ± 4.3**	15.9 ± 5.4**	17.5 ± 4.9*	17.5 ± 4.2*	17.1 ± 4.4*	19.9 ± 4.8	19.8 ± 3.9
SVR (dynes·sec·cm ⁻⁵)	1873 ± 599	1456 ± 451**	1564 ± 418*	1618 ± 423*	1525 ± 478**	1623 ± 470*	1629 ± 509*	1718 ± 505
Double product	11318 ± 1473	12200 ± 3190	12390 ± 2611	11807 ± 1872	11516 ± 2209	11318 ± 2131	11479 ± 1792	11636 ± 2041
TMG (mmHg)	44.6 ± 19.7	47.5 ± 20.6	44.3 ± 20.0	46.9 ± 17.8	46.3 ± 18.3	47.4 ± 16.3	42.5 ± 14.4	47.3 ± 16.6
Plasma drug concentration (μg/ml)	N D	4.0 ± 2.4	2.8 ± 1.8	2.1 ± 1.5	0.9 ± 0.3	0.6 ± 0.2	0.5 ± 0.3	0.4 ± 0.2

Mean ± SD; *** = $p < 0.001$; ** = $p < 0.01$; * = $p < 0.05$

Fig.1. Time course of the percent change in hemodynamic parameters and amrinone plasma concentration (broken line).

- 1) Amrinone (AMN) group consisted of 8 patients (8 males, 49 to 79 years of age): 3 cases with antero-septal, 3 cases with antero-lateral and 2 cases with posterior myocardial infarction.
- 2) Dopamine (DA) group consisted of 15 patients (12 males and 3 females, 56 to 78 years of age): 3 cases with antero-septal, 10 cases with antero-lateral, and 2 cases with posterior myocardial infarction.
- 3) Dobutamine (DB) group consisted of 17 patients (14 males and 3 females, 54 to 84 years of age): 3 cases with antero-septal, 11 cases with antero-lateral, 1 case with lateral, 2 cases with posterior myocardial infarction.

In the AMN group amrinone was administered 1–2 mg/kg i.v. in 3 minutes and hemodynamics and plasma concentration of amrinone (6 cases) were measured before, 5, 10, 15, 30, 60, 90 and 120 minutes after administration. In the DA and DB groups, hemodynamics at the highest value of cardiac index during drip infusion (3–7 µg/kg/min) of DA or DB were compared with pre-treatment hemodynamics.

Hemodynamic effect was measured by right heart catheterization using a flow-directed, balloon-tipped thermodilution catheter to observe heart rate (HR), mean blood pressure (Bpm), cardiac index (CI), stroke volume index (SVI), stroke work index (SWI), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), double product (DP), and transmyocardial pressure gradient (TMG). In addition, plasma concentration of amrinone was measured by the GC-MS (EI) method.

Data were expressed as Mean $\pm$ SD and statistical analysis was performed using Student's t-test for paired data, comparing each value to its corresponding basal control; the Welch t-test was also used for the comparison of drugs.

RESULTS

1) AMN Group

(1) Hemodynamic Changes

Table I summarizes hemodynamic changes before and after intravenous injection of amrinone.

Before administration of amrinone CI was as low as 2.03 ± 0.38 L/min/M², which increased to a high of 2.57 ± 0.43 L/min/M² 5 minutes after administration. This significant increase lasted for up to 60 minutes (2.25 ± 0.34 L/min/M²). Furthermore, SVI and SWI were 23.5 ± 5.1 ml/beat/M² and 39.1 ± 17.2 gm·M/beat/M², respectively before administration, but both increased to a high of 27.9 ± 5.8 ml/beat/M² and 48.0 ± 19.8 gm·M/beat/M², respectively 5 minutes later.

CVP showed a decrease from 9.5 ± 4.6 cm H₂O to 6.0 ± 3.0 cmH₂O and was lowest 5 minutes after injection. 60 minutes later a significant low value (7.2 ± 4.3 cmH₂O) still remained. In the same manner, PCWP was as high as 23.0 ± 2.7 mmHg before injection but significantly decreased 5 minutes after administration to 17.9 ± 4.3 mmHg and to 15.9 ± 5.4 mmHg the lowest level, 10 minutes after administration. A significant decrease was still noted 60 minutes later (17.1 ± 4.4 mmHg). Furthermore, SVR decreased from 1873 ± 599 dynes·sec·cm⁻⁵ before administration to 1456 ± 451 dynes·sec·cm⁻⁵ 5 minutes after administration, maintaining a significant low value (1629 ± 509 dynes·sec·cm⁻⁵) 90 minutes after administration.

HR increased significantly from 88 ± 14 /min

TABLE II HEMODYNAMIC EFFECTS OF DOPAMINE (DA) AND DOBUTAMINE (DB) IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

	DA (n = 15)		DB (n = 17)	
	Before	After	Before	After
HR (beat/min)	92 ± 16	91 ± 18	89 ± 17	96 ± 19*
BPm (mmHg)	83 ± 12	86 ± 13	85 ± 10	86 ± 12
CI (L/min/M ²)	1.77 ± 0.46	2.15 ± 0.55**	1.65 ± 0.47	2.23 ± 0.67***
SVI (ml/beat/M ²)	19.6 ± 5.0	24.2 ± 5.8*	18.8 ± 5.1	23.8 ± 7.0**
SWI (gm·M/beat/M ²)	26.9 ± 8.8	36.9 ± 15.9**	26.1 ± 7.9	37.2 ± 15.9**
CVP (cmH ₂ O)	13.2 ± 4.6	12.2 ± 6.1	12.9 ± 5.3	9.6 ± 5.7**
PCWP (mmHg)	25.1 ± 5.7	22.1 ± 7.7	26.8 ± 6.5	21.6 ± 7.9***
SVR (dynes·sec·cm ⁻⁵)	2073 ± 788	1726 ± 486*	2295 ± 1045	1749 ± 656**
Double product	10059 ± 2580	10601 ± 2988	9713 ± 2588	10883 ± 2995*
TMG (mmHg)	45.6 ± 12.4	48.4 ± 13.6	47.2 ± 11.3	50.5 ± 12.8

Mean ± SD; *** = $p < 0.001$; ** = $p < 0.01$; * = $p < 0.05$

before injection to 94 ± 15 /min 10 minutes after administration. BPm decreased slightly, but the decrease was not statistically significant.

DP, used as an index of myocardial oxygen consumption and TMG, expressing coronary perfusion pressure showed no significant difference before and after administration of amrinone.

(2) Plasma concentration of amrinone

Figure 1 shows the time course of plasma concentration of amrinone (broken line) and percent change in hemodynamic parameters.

Five minutes after CI, SVI and SWI achieved their highest levels (+28.3%, +20.7% and +25.3%, respectively) and CVP and SVR decreased to their lowest levels (−35.9% and −20.9%, respectively), plasma concentration of amrinone showed a markedly high value of 4.04 ± 2.45 µg/ml; 10 minutes later when PCWP decreased to a low of −30.3%, plasma concentration was 2.77 ± 1.81 µg/ml. This value gradually decreased to 2.12 ± 1.52 µg/ml after 15 minutes and to 0.92 ± 0.33 µg/ml after 30 minutes, and 120 minutes later when all hemodynamic parameters showed no significant difference compared with the control value, it was 0.36 ± 0.18 µg/ml.

(3) Adverse effects

Thrombocytopenia and hepatic dysfunction are reported as adverse effects of amrinone,¹²⁻¹³ but in our study using intravenous injection, only one case showed frequent atrial premature beats after administration, and neither thrombocytopenia nor hepatic dysfunction thought to originate from amrinone was noted. Furthermore, no changes on ECG or CPK indicating aggravation of myocardial ischemia and enlargement of infarction size were observed.

2) DA and DP groups

In the DA group (see Table II), CI increased significantly from 1.77 ± 0.46 L/min/M² before administration to 2.15 ± 0.55 after drip infusion, while SVI (from 19.6 ± 5.0 ml/beat/M² to 24.2 ± 5.8 ml/beat/M²), and SWI (from 26.9 ± 8.8 gm·M/beat/M² to 36.9 ± 15.9 gm·M/beat/M²) also increased significantly. SVR decreased significantly from 2073 ± 788 dynes·sec·cm⁻⁵ to 1726 ± 486 dynes·sec·cm⁻⁵, but no significant change was noted in HR, BPm, CVP, PCWP, DP and TMG.

In the DB group (Table II), CI increased markedly from 1.65 ± 0.47 L/min/M² before

Fig. 2. Comparison of effects of amrinone (AMN), dopamine (DA) and dobutamine (DB) on hemodynamic status. (Difference of percent changes in each hemodynamic parameter)

administration to 2.23 ± 0.67 L/min/M² after administration, and SVI and SWI also showed increases. CVP was also significantly lowered from 12.9 ± 5.3 cmH₂O to 9.6 ± 5.7 cmH₂O, as were PCWP (from 26.8 ± 6.5 mmHg to 21.6 ± 7.9 mmHg) and SVR (from 2295 ± 1045 dynes·sec·cm⁻⁵ to 1749 ± 656 dynes·sec·cm⁻⁵). No significant change was noted in BPM and TMG, while HR and DP increased significantly.

3) Comparison between Drugs (Fig. 2)

CI showed the most increase, +35.2%, in the DB group. CI in the AMN and DA groups was +28.3% and +25.1%, respectively. CVP was lowered remarkably in AMN group, -35.9%, DA and DB group figures were -9.8% and -25.8%, respectively. PCWP was also lowered the most in the AMN group (-22.2%). It was lowered -12.0% in the DA group and -19.4% in the DB group. Furthermore, reduction of SVR was nearly on the same level in the AMN and DB groups (-20.9% and -20.0%, respectively), while reduction in the DA group was -13.1%. Change in BPM was -2.6% in the AMN group, +3.6% in the DA group and +1.3% in the DB group, while change in HR was +7.7%, -1.1% and +7.9% in the AMN, DA and DB groups, respectively. These results suggest that amrinone possesses a dominant vasodilating effect in addition to its inotropic effect, that its hemodynamic effect is more similar to that of dobutamine than that of dopamine, and that its vasodilating effect is stronger than that of

dobutamine.

DISCUSSION

(1) Hemodynamic effect of amrinone

Amrinone, synthesized by Leshner and Opalka of Sterling-Wintrop, was reported by Farah and Alousi in 1978 to possess a positive inotropic effect in experiments using atrium and papillary muscle of the cat or the anesthetized dog. Positive inotropic action of amrinone is not inhibited by the beta-blocking agent nor inhibiting Na, K-ATPase; thus its precise mode of action is not yet known.

However, Taira^{2,3} reported that amrinone inhibited the activity of purified PDE obtained from the ventricular muscle of dog, and increased the concentration of ventricular muscle intracellular cyclic AMP; thus it is highly possible that the positive inotropic action of amrinone is based on this mechanism. Taira also noted the marked coronary vasodilatation effect of amrinone. At a dose elevating myocardial contractile force by 50%, coronary blood flow increased by about 100%, which Taira characterized as "cardiotonic coronary vasodilator".

Marked increase of CI and obvious lowering of PCWP were noted in previous clinical studies of amrinone⁴⁻⁹. Most of the patients in these studies did not show sufficient improvement in hemodynamics and subjective symptoms upon dosage of digitalis and diuretics. Benotti et al⁴ investigated the effect of amrinone in eight

Fig.3. Hemodynamic effects of amrinone (AMN), dopamine (DA), dobutamine (DB) and isosorbide dinitrate (ISDN). Differences of the percent changes in CI, PCWP and CVP.

patients with congestive heart failure. They found a significant increase in CI and a significant lowering in LVFP. In our study, significant increases in CI, SVI and SWI as well as a significant lowering of PCWP, CVP and SVR were observed. These effects were most noticeable five minutes after intravenous injection and lasted for about 60 minutes.

Positive inotropic agents increase myocardial oxygen consumption. When applied to patients with acute myocardial infarction, they may aggravate myocardial ischemia and enlarge the range of infarction. However, reduced left ventricular filling pressure due to the vasodilating effect of amrinone relieved left ventricular wall tension and moderated increase of myocardial oxygen consumption accompanied by positive inotropic action.⁵

Naccarelli et al⁹, who studied the arrhythmogenic action of amrinone, reported that no significant difference in frequency of ventricular tachycardia induced by programmed electrical stimulation or occurred spontaneously and that the arrhythmogenic effect of this preparation was slight.

We studied acute myocardial infarction cases, among whom HR increased slightly after administration of amrinone. Neither aggravation of ischemia nor extension of infarction size was observed on ECG and time course of CPK, and with regard to arrhythmia, only one case showed frequent occurrence of atrial premature beats immediately after intravenous injection. Accordingly amrinone is considered to be safe intra-

venous injection even in the acute stage of myocardial infarction.

(2) Comparison between drugs

Both dopamine and dobutamine have a positive inotropic effect with intermediary sympathetic beta-receptors, but there are several differences between these drugs. According to the results of a comparative study carried out at 33 institutions in Japan,¹⁰ a marked decrease of PCWP is indicated a specially with dobutamine.

Klein et al⁷, comparing the effect of amrinone with that of dobutamine, observed that intravenous drip infusion of amrinone at 10–40 $\mu\text{g/kg/min}$ increased CI and lowered PCWP to nearly the same level as that achieved upon administration of dobutamine at 11.8 $\mu\text{g/kg/min}$ and concluded that comparatively similar activities are displayed by both preparations. On the other hand, Wilmshurst et al⁸ reported that the effect of amrinone was similar to that of sodium nitroprusside, since the major action of amrinone is not cardiotoxic but vasodilational. In accordance with their opinion, if amrinone is to be a PDE inhibitor, as is the case with theophylline, a positive inotropic effect may depend on release of endogenous catecholamine. However, their results revealed that CI increase by amrinone far exceeded that of sodium nitroprusside.

Figure 3 shows the characteristics of each drug, summarizing the results together with those for ISDN from our previous study.¹¹ Amrinone would be positioned just between catecholamines and ISDN, most likely accompa-

nying use the of ISDN and dobutamine. Accordingly, this preparation could be positioned as a "positive inotropic agent similar to a vasodilator".

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