Constant Intravenous Infusion of Chlorpromazine for Both Sedation and After-Load Reduction in Postcardiotomy Patients under Intraaortic Balloon Pumping

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SUMMARY

Continuous intravenous infusion of chlorpromazine (CPZ) was used for both sedation and after-load reduction in 13 Japanese patients (Group 1) supported by an intraaortic balloon pump (IABP) after open-heart surgery. CPZ was initiated at a dose of 0.05 mg/kg/hr and was maintained in an approximate dose range of 0.1–0.3 mg/kg/hr depending on individual patient needs. The drug was administered until the IABP was removed and the blood gases were normalized. During this period, the patients slept well and the trigger lines for the IABP were sufficiently secured. In order to evaluate the hemodynamic changes in these patients, the 10 patients who were supported by the IABP and given continuous intravenous sodium thiamylal (ST) for sedation in an approximate dose range of 1–2 mg/kg/hr (Group 2) were employed as controls. After administration of CPZ, the systemic vascular resistance, central venous pressure, and left atrial pressure decreased, while the cardiac output increased. The predicted untoward effects of CPZ, such as tachycardia and hypotension, were minimal. In the ST group, by contrast, the cardiac output decreased somewhat in association with the increase in systemic vascular resistance. From these results, we conclude that constant intravenous CPZ is beneficial for postcardiotomy patients who have severe low cardiac output syndrome and are supported with IABP, by both successfully sedating the patients and reducing ventricular after-load.

Key Words:

Open heart surgery Vasodilator Major tranquilizer Post-cardiotomy delirium Postoperative psychosis Low cardiac output syndrome Denopamine

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AN intraaortic balloon pump (IABP) is one of the most beneficial devices^{1),2)} for the treatment of patients with severe low cardiac output syndrome (LOS) after cardiac surgery. Since this device requires continuous monitoring of electrocardiograms (ECG) or arterial pressures as a trigger to determine the optimal timing of the inflation and deflation of the balloon,¹⁾ it is extremely important to secure these monitoring lines from any movement that might possibly cause electrical noise. Patients with severe LOS, however, tend to experience postcardiotomy delirium³⁾⁻⁵⁾ and to remove themselves from their life-lines, including the IABP catheter, arterial pressure line, central venous pressure (infusion) line, left atrial pressure line, Swan-Ganz catheter, intratracheal respiratory tube, and intrapericardial drains, when adequate sedatives are not given.

For sedating such critically ill patients, various drugs may be used, including barbiturates, opioids, major and minor tranquilizers, and muscle relaxants.⁶⁾ Before 1988, we had extensively used a bolus IV injection of diazepam, buprenorphine, pentazocine, haloperidol, morphine, fentanyl, and/or pethidine alone or combined with pancuronium bromide, in order to sedate these patients. The bolus injections, however, often caused harmful hemodynamic changes in patients with severe LOS. Moreover, the effectiveness of the drugs is usually of short duration.

Since 1988, we have been using a continuous intravenous infusion of chlorpromazine (CPZ) for patients with IABP. This drug was chosen because it is a well-known major tranquilizer and its α -blocking action appears to be appropriate for adequately reducing the after-load of the damaged heart.⁷⁾⁻⁹⁾ On the other hand, continuous intravenous infusion with sodium thiamylal (ST) has also been used at our institution, especially for patients with air embolism or ischemic brain damage suffered during cardiopulmonary bypass.¹⁰⁾⁻¹²⁾ This method, however, has also been extended since 1987 to patients with IABP in order to sedate them. Although both drugs were effective in sedating the patients, CPZ was found to be even more effective than ST in improving the hemodynamics of the patients in the present study.

PATIENTS AND METHODS

Patients: Twenty-three Japanese patients who underwent open heart surgery from June 1988 to June 1990 at Kyushu University Hospital and had suffered severe LOS after weaning from cardiopulmonary bypass were included in this study. All of the patients were treated with an IABP (K-2000, Kontron, Everett, Mass.) either during the operation or after ad-

mission to the intensive care unit (ICU). We used an IABP when weaning from cardiopulmonary bypass was difficult because of the following conditions: systolic aortic pressure <80 mmHg, left atrial pressure >15 mmHg, cardiac index <2.0 l/min/m², and dopamine plus dobutamine >10 μ g/kg/min. Neither norepinephrine nor epinephrine was used until IABP was found to be insufficient to support the diseased heart. Out of 23 patients, 13 were given continuous CPZ (Contomin 5 mg/ml; Yoshitomi, Osaka, Japan) in a dose range of 0.05–0.29 mg/kg/hr (Group 1). The drug was started with a small dose (usually, 0.05 mg/kg/hr) and then gradually increased up to the dose level at which the patients were able to sleep well but awoke with a cough reflex at the time of suctioning of sputa and tracheo-bronchial toilet. When CPZ was started, the continuous intravenous infusion of sodium nitroprusside (SNP; 0.48 ± 0.23 μ g/kg/min) was discontinued gradually over several hours. For the control group (Group 2), 10 patients were given continuous ST (Isozol; Yoshitomi) in a dose range of 0.55–2.15 mg/kg/hr. The drug (25 mg/ml) was usually started at a rate of 1 mg/kg/hr and then was gradually increased as well. The drugs were infused by a microinfusion pump (Infusion pump 235; Atom, Tokyo).

IABP was weaned when the cardiac index increased to >2.5 l/min/m² under <5 μ g/kg/min of dopamine plus dobutamine.

In both of the groups, IABP was usually weaned first, followed by weaning from the respirator. The sedatives were discontinued before weaning from the respirator was initiated.

Measurements: In all of the patients, a Swan-Ganz catheter was inserted either before or during the operation. Cardiac output (the mean of 3 trials) was examined by the thermodilution technique right before, and approximately 5, 12, and 24 hours after starting the drugs. Thereafter, cardiac output was measured usually twice a day. At the time of cardiac output measurement, the heart rate, mean aortic pressure, central venous pressure, left atrial pressure (pulmonary capillary wedge pressure), and mean pulmonary arterial pressure were all recorded. A hemodynamic calculation was performed using the HP component monitoring system (Hewlett-Packard, Waltham, Mass.).

Statistics: Student's t-test was performed to compare parametric data that were expressed as the mean $\pm$ SD in 2 groups. The chi-square test with Yates' correction was also used to compare the incidences in 2 groups. To compare the hemodynamic data, a two-way analysis of variance (ANOVA) was performed first.¹³⁾ Only when the variance was significant was the modified Student's t-test performed.^{13),14)} For multiple comparisons, the Bonferroni correction was used.^{13),14)} P value was calculated by means

of a personal computer (PB-700, Casio, Tokyo). A *p* value of <0.05 was taken to be significant.

RESULTS

Profile of the patients: The details of the patients in Group 1 (CPZ; *n*=13) and Group 2 (ST; *n*=10) are presented in Table I. As predicted from the use of IABP, the patients were exposed to a prolonged period of cardiac arrest and cardiopulmonary bypass in both groups. The dose of dopamine plus dobutamine was $>10 \mu\text{g/kg/min}$ in most of the patients in both groups at the beginning of the study. The vasodilators used right before this study were nitroglycerin (NTG) and sodium nitroprusside (SNP). In Group 1, SNP was replaced with CPZ, and was discontinued within several hours, whereas it was continued as previously given in Group 2. The differences in these data in the 2 groups were statistically insignificant. The New York Heart Association functional class, however, was more severe in Group 1 than that in Group 2 (Table I).

General outcome of the treatment: In Group 1, IABP was used for 6.1 ± 3.4 (mean $\pm$ SD) days (Table II). CPZ in a maximal dose of 0.16

Table I. Profiles of the Patients

	Group 1	Group 2	P-value
	CPZ	ST	
No. of patients	13	10	—
Male/Female	7/6	2/8	NS
Age (years)	54.6 ± 14.3 (range 19–70)	57.6 ± 10.4 (range 38–67)	NS
Diagnosis			
VHD	6	5	
IHD	4	3	
VHD+IHD	3	0	
CHD	0	1	
ANEURYSM	0	1	
NYHA	3.5 ± 0.5	2.7 ± 1.0	0.020
AXT (min)	165.9 ± 76.9	149.6 ± 101.8	NS
CPBT (min)	254.2 ± 112.3	275.9 ± 205.2	NS
DOP+DOB ($\mu\text{g/kg/min}$)	11.5 ± 4.6	12.1 ± 6.6	NS
NTG ($\mu\text{g/kg/min}$)	0.65 ± 0.28	0.63 ± 0.30	NS
SNP ($\mu\text{g/kg/min}$)	0.48 ± 0.23	0.47 ± 0.25	NS

CPZ=chlorpromazine; ST=sodium thiamylal; NS=not significant; VHD=valvular heart disease; IHD=ischemic heart disease; CHD=congenital heart disease; NYHA=New York Heart Association; AXT=aortic cross clamping time; CPBT=cardiopulmonary bypass time; DOP=dopamine; DOB=dobutamine; NTG=nitroglycerin; SNP=sodium nitroprusside.

Table II. General Outcome of the Treatment

	Group 1	Group 2	P-value
	CPZ	ST	
No. of patients	13	10	—
Use of IABP (days)	6.1 ± 3.4	7.3 ± 3.7	NS
(range)	(3–15)	(3–14)	
Use of the drug (days)	9.8 ± 10.6	5.3 ± 4.0	NS
(range)	(3–32)	(2–14)	
Maximal dose (mg/kg/hr)	0.16 ± 0.08	1.31 ± 0.54	—
(range)	(0.05–0.29)	(0.55–2.15)	
Use of respirator (days)	16.1 ± 13.9	9.9 ± 5.6	NS
(range)	(3–40)	(4–17)	
ICU stay (days)	17.6 ± 14.6	10.7 ± 5.1	NS
(range)	(4–43)	(5–18)	
Hospital death	1/13	2/10	NS

CPZ=chlorpromazine; ST=sodium thiamylal; NS=not significant; IABP=intraaortic balloon pump; ICU=intensive care unit.

± 0.08 mg/kg/hr was given for 9.8 ± 10.6 days. A respirator was necessary for 16.1 ± 13.9 days. The patients were discharged from ICU at 17.6 ± 14.6 days after the operation. Hospital death was observed in 1 patient out of the 13. The patient, with aortic and mitral regurgitation due to giant cell aortitis, had undergone a double valve replacement with Hancock bioprostheses and tricuspid annuloplasty 8 years earlier. The patient showed severe low cardiac output syndrome and acute renal failure because of aortic and mitral periprosthetic leakage (at first these were diagnosed as primary tissue failure of the bioprostheses) due to acute exacerbation of giant cell aortitis. After a double valve replacement with St. Jude Medical valves, the patient died of multiple organ failure 21 days after operation.

In Group 2, by contrast, IABP was required for 7.3 ± 3.7 days. ST in a maximal dose of 1.31 ± 0.54 mg/kg/hr was given for 5.3 ± 4.0 days. A respirator was required for 9.9 ± 5.6 days. The postoperative stay in the ICU was 10.7 ± 5.1 days. Two patients died in this Group. Both of the patients had undergone a double valve replacement with bioprostheses and tricuspid annuloplasty previously, and had a double valve replacement with St. Jude Medical valves in an elective or emergent fashion, respectively. Preoperative complication of liver cirrhosis or acute renal failure triggered the occurrence of multiple organ failure in each of these cases. The patients died 18 and 10 days after operation, respectively.

Despite the preoperatively more severe conditions in Group 1, the use of IABP appeared to be shorter in Group 1 than that in Group 2, although this difference did not attain statistical significance (Table II). On the

contrary, longer sedation, respirator and ICU stay periods were required for Group 1 than for those in Group 2. This discrepancy may be ascribed to pulmonary dysfunction and acute renal failure which were experienced for prolonged periods in 2 of the Group 1 patients.

Hemodynamic changes in CPZ- or ST-treated patients: The hemodynamic changes after CPZ or ST treatment are presented at 3 different time points, i.e., right before, 3–6 hours after, and 18–30 hours after each drug was initiated (Figs. 1–3). The heart rate and mean aortic pressure did not significantly change in either of the groups (Fig. 1). In the CPZ group (Group 1), the heart rate appeared to increase while the mean

Fig. 1. Hemodynamic changes after chlorpromazine or sodium thiamylal administration (1). HR=heart rate; mAoP=mean aortic pressure; CPZ (○, n=13); ST (●, n=10). Two-way ANOVA for upper panel; $p=0.551$ (drugs), 0.125 (time points), and 0.580 (interaction). Two-way ANOVA for lower panel; $p=0.083$ (drugs), 0.53 (time points), and 0.933 (interaction).

Fig. 2. Hemodynamic changes after chlorpromazine or sodium thiamylal administration (2). CVP=central venous pressure; LAP=left atrial pressure; CPZ (○, n=13); ST (●, n=10). Two-way ANOVA for upper panel; $p=0.00003$ (drugs), 0.550 (time points), and 0.556 (interaction). (*), $p=0.0014$ by the modified t-test. Two-way ANOVA for lower panel; $p=0.016$ (drugs), 0.990 (time points), and 0.321 (interaction). (*), $p=0.016$ by the modified t-test.

Fig. 3. Hemodynamic changes after chlorpromazine or sodium thiamylal administration (3). CI=cardiac index; SVRI=systemic vascular resistance index; LCWI=left cardiac work index; CPZ (○, n=13); ST (●, n=10). Two-way ANOVA for upper panel; $p=0.002$ (drugs), 0.047 (time points), and 0.030 (interaction). (*), $p<0.05$ by the modified t -test. Two-way ANOVA for middle panel; $p=0.00002$ (drugs), 0.802 (time points), and 0.099 (interaction). (*), $p<0.01$ by the modified t -test. Two-way ANOVA for lower panel; $p=0.442$ (drugs), 0.605 (time points), and 0.186 (interaction).

aortic pressure decreased. These changes, however, were not statistically significant. The preloads of both the right and left ventricles were higher in Group 1 than those in Group 2 at the beginning of drug-treatment (Fig. 2). Such over-loading of the ventricles was gradually corrected after CPZ treatment (Fig. 2).

As shown in Fig. 3, the cardiac output in Group 1 gradually increased despite the decrease in the preloads (Fig. 2), while systemic vascular resistance decreased (Fig. 3). By contrast, in the ST-treated group (Group 2), the cardiac output tended to decrease while the systemic vascular resistance increased (Fig. 3). Meanwhile, left cardiac work did not change significantly in either of the groups during this period, although that of Group 1 appeared to gradually increase.

CASE

A 19-year-old woman with infective endocarditis due to *Streptococcus sanguis* and resulting acute mitral regurgitation was admitted to our department in September 1988 because of increasing left heart failure and emacia-

tion (height 160 cm, weight 36 kg). Although her endocarditis seemed to be almost controlled (CRP, max 5.4 mg/dl $\rightarrow$ 0.5 mg/dl; WBC, max 15880/mm³ $\rightarrow$ 6990/mm³) by the appropriate antibiotic therapy with 18 million units/day of benzylpenicillin for 20 days, she was still in New York Heart Association functional class IV after continuous intravenous administration of 5 μ g/kg/min of dobutamine for 12 days. During surgery, the anterior and posterior leaflets of the mitral valve showed edematous changes. The posterior chordae of the anterior leaflet were torn. Mitral valve replacement with a 27 mm St. Jude Medical valve was performed under aortic cross clamping for 65 min and cardiopulmonary bypass for 110 min. After weaning from the cardiopulmonary bypass with 8 μ g/kg/min of dobutamine plus 6 μ g/kg/min of dopamine, the cardiac index decreased from 2.60 l/min/m² at the end of cardiopulmonary bypass to 1.35 l/min/m² in 1 hour. IABP, therefore, was employed in the operating room.

In the ICU, severe LOS continued (Fig. 4). The systemic vascular resistance was gradually increased despite the use of 0.6 μ g/kg/min of SNP and 0.6 μ g/kg/min of NTG. To maintain mean aortic pressure of >70 mmHg, 18–20 mmHg of left atrial pressure and central venous pressure in addition to 8 μ g/kg/min of dopamine plus 10 μ g/kg/min of dobutamine were required. An oral catecholamine, denopamine (Kalgut; Tanabe, Osaka), at a dose rate of 10 mg/8 hr was administered via the nasogastric tube. Urine output was 1–2 ml/kg/hr under the extensive use (305 mg in the first 14 hr) of furosemide. Blood gas data including base excess were within normal

Fig. 4. Representative clinical course in a patient given constant intravenous chlorpromazine. See text for details.

limits under respirator conditions of FIO_2 0.3 and a ventilatory volume of 6 l/min.

In the early morning of postoperative day (POD) 1, the patient awoke, and was quite nervous, anxious, and restless. The patient communicated frequently with the nurse on duty by exchanging written notes, during which monitoring signals of ECG and radial arterial pressure tended to be noisy. Therefore, 2.5 mg/hr (0.07 mg/kg/hr) of CPZ was started and was increased up to 10 mg/hr (0.28 mg/kg/hr) after an hour, while SNP was reduced and discontinued after 6 hours in order to maintain a constant systemic mean arterial pressure of >70 mmHg. The patient slept well and was awakened only during the suctioning of sputa.

After CPZ infusion was started, the systemic vascular resistance decreased and the cardiac output increased markedly. The left atrial and central venous pressures also decreased over time. CPZ was continued for approximately 3 days. First the respirator and then the IABP were removed on POD 4 (Fig. 4). The patient was discharged from the ICU on POD 5.

DISCUSSION

Vasodilator therapy is commonly administered after cardiac operations, especially for patients with left ventricular failure.⁷⁾⁻⁹⁾ Vasodilators reduce afterload while optimizing preload. Reduction in systemic vascular resistance leads to lower wall tension, resulting in less left ventricular work (lower myocardial oxygen requirements) and a more favorable myocardial O_2 balance. The same end result occurs through decreasing the preload.⁹⁾ As long as adequate filling pressures are maintained, the maximal benefit of this therapy is obtained.^{8),9)} In this sense, continuous intravenous CPZ provided an excellent effect on the ill heart supported by IABP plus catecholamines in the present study. Stinson et al⁷⁾ reported that CPZ decreased systemic vascular resistance and increased cardiac output. As an untoward effect, CPZ increased heart rate by 20% over the pretreatment value.⁷⁾ In their study, however, CPZ was given by repeated bolus injections of 2.5 mg intravenously (average total dose 10.3 mg). In the present study, no significant change in systemic arterial pressure or heart rate was observed, although we used an average dose of 190 mg/day (range; 59–370 mg). This difference is probably attributable to the different injection methods. In our method, moreover, another vasodilator, SNP, was replaced with CPZ when SNP was used before CPZ. Taken together, these facts suggest that CPZ can be safely and beneficially used as a vasodilator by infusing it intravenously in a constant fashion instead of administering it in a bolus injection.

The production of sedation and the reduced control over hemodynamics compared with SNP or NTG may be major causes for the less frequent use of CPZ than in the past for its vasodilating effect.⁹⁾ In the IABP patients, however, the production of sedation was considered to be perfectly suitable, because it enabled their life lines, including the triggers of IABP, to be well secured so that the IABP functioned steadily. Moreover, this drug did not affect the cough reflex. Thus, the suctioning of sputa was not impaired. The decreased control of hemodynamics could be minimized by infusing the drug continuously in a small starting dose. In severe LOS patients, the support with IABP and catecholamines tends to be prolonged as presented in the present study (Table II). Therefore, concomitant vasodilator therapy is also necessary for a prolonged period. In such situations, CPZ appeared to cause much less tolerance than SNP or NTG.

The constant intravenous barbiturate, ST, was also deemed effective in sedating the patients with IABP. This drug, however, has a negative inotropic action, and increases the peripheral vascular resistance,¹⁵⁾ although these changes were not statistically significant in the present study (Fig. 3). Barbiturates are usually used for patients with acute brain insults, in order to extend rudimentary neurological functions during severe hypoxia, limit the area of infarction following cerebral vascular occlusion, and reduce intracranial pressure.¹⁶⁾ After cardiac surgery, these drugs are considered to be beneficial for patients with air embolism during cardiopulmonary bypass.^{10),11)} As predicted from the main effect (suppression of metabolism) on the brain, ST may be negatively inotropic to the heart by suppressing its metabolism, which is suggested by the marginal decrease in left cardiac work (Fig. 3). It is difficult to draw a conclusion as to the ultimate superiority of the 2 drugs, CPZ or ST, in reducing patient mortality. However, CPZ was clearly superior to ST, at least in improving the hemodynamics of patients with severe LOS.

Although the maximum parenteral dose of CPZ for Japanese adults has been indicated to be 400 mg/day,¹⁷⁾ this drug is considered to be remarkably safe and adult patients have survived doses of CPZ of up to 10 g.¹⁸⁾ In the present study, no severe untoward effects of CPZ such as refractory hypotension, extrapyramidal effects, and agranulocytosis, were observed. In order not to exceed the maximum dose of (CPZ), in this study we utilized doses of less than 370 mg/day. In some patients, however, CPZ >300 mg/day was not always sufficient to keep them constantly asleep. In such patients we added other sedatives such as diazepam or fentanyl administered in a bolus injection, especially at night. Further increments in the dose of CPZ may prove to be possible for these patients.

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