Effects of Dibutyryl Cyclic AMP on Patients with Severe Heart Failure

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SUMMARY

Dibutyryl cyclic AMP was administered to 2 patients with severe congestive heart failure. After an intravenous drip infusion of dibutyryl cyclic AMP (300 mg/40 min), marked diuresis and mild improvement of the patients' physical activity occurred. The cardiac index increased and both systemic vascular resistance and pulmonary capillary wedge pressure decreased. Blood glucose and plasma insulin increased simultaneously, while plasma free fatty acid decreased during the infusion. A continuous intravenous micro-infusion of dibutyryl cyclic AMP (300 mg/24 h) also exerted diuresis and improved physical activity. The hemodynamic and metabolic effects of dibutyryl cyclic AMP are expected to be beneficial to a failing heart.

Additional Indexing Words:
Cardiac index  Blood glucose  Plasma insulin  Plasma free fatty acid  Continuous intravenous micro-infusion

Cyclic 3', 5' adenosine monophosphate (cyclic AMP) has been shown to play an important role as an intracellular second messenger of various hormones, especially catecholamines. However, exogenous cyclic AMP does not exert a catecholamine-like effect because it can hardly pass the cell membrane. A derivative of cyclic AMP, N6-O2'-dibutyryl cyclic 3', 5' adenosine monophosphate (dibutyryl cyclic AMP), is resistant to enzymatic hydrolysis by phosphodiesterase and easily passes through the cell membrane because of its lipid solubility. After passing the cell membrane, dibutyryl cyclic AMP is deacylated to cyclic AMP and its accumulation within the cell may result in a catecholamine-like effect, or dibutyryl cyclic AMP is deacylated to N6-monobutyryl cyclic AMP, which is a strong...
phosphodiesterase inhibitor, and it may decrease the rate of degradation of endogenous cyclic AMP.\(^6\)

In patients with congestive heart failure, the plasma catecholamine level increases gradually as the heart failure progresses.\(^7\) However, both the sensitivity of \(\beta\)-adrenergic receptors\(^8\) and the activity of adenylate cyclase\(^9\) have been suggested to be reduced in patients with congestive heart failure. It may consequently be assumed that intramyocardial cyclic AMP is depleted\(^9\) and exogenous catecholamines cannot always enhance intracellular cyclic AMP level (i.e. sometimes ineffective) in severe congestive heart failure. Administration of dibutyryl cyclic AMP may counteract the decreased intracellular cyclic AMP level in heart failure because it bypasses the \(\beta\)-adrenergic receptor system. Therefore, we administered the compound to 2 patients whose congestive heart failure was not improved by the conventional therapy.

**Case Reports**

**Case 1.** A 49-year-old male with a history of rheumatic fever at age 14 was admitted to the Nagoya University Hospital in December 1980 because of severe congestive heart failure. He first experienced an episode of heart failure at age 37, and his heart failure was gradually aggravated. In April 1978, cardiac catheterization was performed. Mean pulmonary capillary wedge pressure, pulmonary arterial pressure and systemic arterial pressure were 22, 85/40 and 100/60 mmHg, respectively. Aortography showed moderate aortic regurgitation (Sellers 2\(^+\)). According to the findings of cardiac catheterization, ultrasonic cardiogram and phonocardiogram, the patient was diagnosed to have the rheumatic valvular disease consisting of mitral stenosis and regurgitation and aortic stenosis and regurgitation with functional tricuspid regurgitation. The patient rejected the operation.

The physical examination on admission revealed an irregular pulse rate of 70/min; the blood pressure was 88/62 mmHg. The auscultation of the chest revealed moist rales on both middle and lower lung fields. Holosystolic murmur (4\(^+\)/6\(^+\)) and diastolic rumble (4\(^+\)/6\(^+\)) were heard at the cardiac apex and diastolic blowing murmur (3\(^+\)/6\(^+\)) was heard at the 4th left sternal border. Mitral opening snap was also heard. The pulsatile liver edge was palpable at 4 finger breadths below the xiphoid. A moderate amount of ascites and pretibial pitting edema were present. A chest roentgenogram revealed a cardio-thoracic ratio (CTR) of 76\% and a dominant pulmonary artery and right ventricle. An electrocardiogram showed marked right ventricular hypertrophy with the rhythm of atrial fibrillation. Serum total bilirubin was 2.8 mg/100 ml, blood urea nitrogen 25 mg/100 ml, creatinine 1.3 mg/100 ml,
Fig. 1. Effects of intravenous dibutyryl cyclic AMP on plasma free fatty acid (FFA), insulin, cyclic AMP (c-AMP), and blood glucose levels in Cases 1 and 2. Three hundred mg of dibutyryl cyclic AMP was dissolved in 200 ml of saline and administered over 40 min (0.13-0.15 mg/Kg/min) by intravenous drip infusion.

total cholesterol 155 mg/100 ml, and free fatty acid (FFA) 0.28 mEq/L. Methylidigoxine (0.1 mg), furosemide (160 mg), triamterene (200 mg), and methyclothiazide (5 mg) were administered daily. However, the patient’s physical activity remained NYHA Class 4°. Dopamine (8 μg/Kg/min) was ineffective. After obtaining informed consent, 300 mg of dibutyryl cyclic AMP (Daiichi Pharmaceutical Co) was administered over 40 min (0.15 mg/Kg/min) to the patient by intravenous drip infusion to improve the severe heart failure. A mild fall of both systolic and diastolic blood pressure and a mild increase in heart rate were observed during the infusion. Laboratory data immediately after the infusion revealed increases in both blood glucose and plasma insulin, and decreased plasma FFA (Fig. 1). The infusion was performed 11 times. The urine volume increased markedly on the first day of the infusion, but it gradually decreased when administered successively. Therefore, the infusion was performed intermittently (Fig. 2). The patient sometimes complained of slight palpitation during the infusion and mild lassitude due to diuresis after the infusion, but they were tolerated well. Arrhythmogenic effects of the drug were not observed. The physical activity of the patient was mildly improved. To detect better methods of dibutyryl cyclic AMP administration, we administered the compound continuously in a very low dose. Three hundred mg of dibutyryl cyclic AMP was dissolved in 5 ml of saline and injected intravenously at a rate of 4.2 μg/Kg/min with a constant micro-infusion pump (Sharp MP-21) for a period of 3 days. During the micro-infusion, the blood pressure was unchanged but the heart rate and the urinary volume increased. The patient complained of mild lassitude due to diuresis, but it was tolerated well. After the micro-
Fig. 2. Diuretic effects of intravenous dibutyryl cyclic AMP in Case 1. An arrow represents the time of administration of dibutyryl cyclic AMP (300 mg/40–90 min). The vertical shaded bar represents urinary volume (U. V.) for the day. The solid line shows the body weight (B. W.) of the patient. Peroral water intake was between 900 and 1,200 ml/day throughout the period shown in this figure.

Fig. 3. Effects of intravenous dibutyryl cyclic AMP, administered continuously with a micro-infusion pump in Case 1. Three hundred mg of dibutyryl cyclic AMP was dissolved in 5 ml of saline and administered at a rate of 4.2 μg/Kg/min for a period of 3 days. Arrows show the period of administration. The obliquely hatched area, upper solid line, lower solid line and vertically hatched bar represent the systemic blood pressure (B. P.), heart rate (H. R.), body weight (B. W.), and urinary volume (U. V.) for the day, respectively. Peroral water intake was between 1,000 and 1,100 ml/day throughout the period shown in this figure.

infusion, ascites, hepatomegaly, and edema all decreased and the patient reported improved physical activity (Fig. 3). Laboratory data showed decreased FFA and unchanged blood glucose and insulin during the micro-in-
Case 2. A 23-year-old male was admitted to the Nagoya University Hospital in May 1981 because of congestive heart failure. He had experienced episodes of congestive heart failure since December 1980 and had been admitted to a hospital. A diagnosis of congestive cardiomyopathy had been made according to ultrasonic findings. His heart failure aggravated gradually and he was referred to the Nagoya University Hospital.

The physical examination on admission revealed a regular pulse rate of 110/min; the blood pressure was 94/80 mmHg. The auscultation of the chest revealed holosystolic murmur (2°/6°) on cardiac apex and no rales on lung fields. The liver edge was palpable at 2.5 finger breadths below the xiphoid. Ascites and peripheral edema were not present. A chest roentgenogram revealed a CTR of 58% and a dominant left ventricle. An electrocardiogram showed sinus tachycardia, left atrial overload, and ischemic ST-T changes in leads V₅ and V₆. An ultrasound cardiogram showed a very wide left atrium and left ventricle, with poor motion of the left ventricular posterior wall and interventricular septum (ejection fraction: 28%).

Diuretics and digitalis were administered, but the patient’s physical activity remained NYHA Class 3°. After obtaining informed consent, 300 mg of dibutyryl cyclic AMP was administered to the patient over 40 min (0.13 mg/Kg/min) by intravenous drip infusion, and both hemodynamic and metabolic parameters were recorded (Table I). During the infusion, the systolic blood pressure was elevated and the pulse pressure increased, while the heart rate unchanged. The cardiac index also showed a two-fold increase, corresponding to the marked reduction of the systemic vascular resistance, and the pulmonary capillary wedge pressure decreased. Drug-induced arrhy-

<table>
<thead>
<tr>
<th>Time after starting the infusion (min)</th>
<th>0 (before)</th>
<th>20</th>
<th>40</th>
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<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>80/66</td>
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<tr>
<td>HR (/min)</td>
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<td>109</td>
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<tr>
<td>PCWP (mmHg)</td>
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<tr>
<td>CI (/min/ml)</td>
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<td>1.77</td>
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<td>SVR (dynes-sec-cm⁻²)</td>
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<td>1620</td>
<td>1130</td>
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</table>

Three hundred mg of dibutyryl cyclic AMP was dissolved in 200 ml of saline and administered over 40 min (0.13 mg/Kg/min) by intravenous drip infusion.

Abbreviations: SBP = systemic blood pressure; HR = heart rate; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SVR = systemic vascular resistance.
thmia was not observed, and the patient had no complaint. Laboratory tests again revealed increased blood glucose and insulin levels and decreased plasma FFA (Fig. 1). The patient's physical activity was mildly improved.

**DISCUSSION**

Dibutyryl cyclic AMP has been shown to have positive inotropic,11) chronotropic and vasodilative effects11),12) in animal experimental models. In addition to cardiovascular effects, dibutyryl cyclic AMP has been reported to affect renal function12),13) and the metabolism of glycogen and fat.3),4),14) Although the effect of dibutyryl cyclic AMP seems to resemble that of isoproterenol (β-adrenergic stimulant), they are not identical because dibutyryl cyclic AMP elevates tissue cyclic AMP level independent of the β-adrenergic receptor system and may affect tissues or organs which have no β-receptors. In our patients, the administration of dibutyryl cyclic AMP increased blood glucose and plasma insulin levels simultaneously. These effects are similar to isoproterenol15) and may be compared to the "intrinsic" glucose-insulin therapy, which may be beneficial to the ischemic and failing heart.16) Depression of plasma free fatty acid (FFA) concentration may also be beneficial because increased plasma FFA level is an arrhythmogenic factor.17) Elevation of blood glucose may be due to the enhancement of glycogen breakdown and the inhibition of glyconeogenesis by the elevated tissue cyclic AMP level.3),4),14) While the stimulation of insulin secretion may be due either secondarily to the elevated blood glucose level or primarily to the stimulation of pancreatic islet cells by dibutyryl cyclic AMP,18) Depression of the plasma FFA level is one of the characteristic effects of dibutyryl cyclic AMP14) and is opposite to the effect of catecholamines.15) Dibutyryl cyclic AMP had a significant diuretic effect in our patients when administered both in normal doses and in very low doses (micro-infusion). The hemodynamic effects of dibutyryl cyclic AMP, monitored in Case 2, consisted of a marked reduction of the systemic vascular resistance and improvement of the cardiac index with increased pulse pressure and unchanged heart rate. Vasodilative effects of the drug seemed to be dominant in this patient with congestive cardiomyopathy. Although one of the patients (Case 1) felt palpitations and lassitude due to diuresis both during and after the administration of dibutyryl cyclic AMP, the complaints were minor and were tolerated well. Arrhythmogenic effects of the drug were not observed. Thus, dibutyryl cyclic AMP seems to exert characteristic and beneficial effects on hemodynamics and metabolism in certain patients with severe congestive heart failure.
ACKNOWLEDGMENT

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REFERENCES