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Abstract

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KEYWORDS: isosorbide dinitrate, syncopal attack hypotension

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A PATIENT WITH REPEATED SYNCOPAL ATTACKS AFTER USING ISOSORBIDE DINITRATE

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Abstract. The case of a patient with repeated attacks of collapse induced by sublingual isosorbide dinitrate is reported. The patient was an 81 year-old female who was admitted to Yura Hospital because of attacks of precordial pain. Several minutes after the sublingual administration of isosorbide dinitrate (10 mg) for an anginal attack, she developed a sensation of general weakness, and thereafter became unconscious. Arterial blood pressure fell and became unmeasurable. Electrocardiograms recorded during the syncopal attack showed sinus tachycardia and significant elevation of ST-segment in right precordial leads. In response to a drip infusion of noradrenaline, arterial blood pressure returned to normal with recovery of consciousness. Two similar syncopal attacks induced by sublingual isosorbide dinitrate occurred in the next three days. These attacks were not due to augmentation of the vagal reflex. Decrease of venous return probably was the primary etiological factor.

Key words: isosorbide dinitrate, syncopal attack hypotension

Ever since the positive effect of nitroglycerin on angina pectoris was first reported by Murrel (1) in 1879, nitrite preparations have played an important role in the treatment of angina pectoris. One of the important actions of nitrite is the dilatation of blood vessels due to its effect on smooth muscle. This action is said to be pronounced in relatively large veins and somewhat weaker in small blood vessels such as arterioles and venules (2-3). Increase in venous capacitance results in reduction of blood volume returning to the heart and causes a fall in preload of the left ventricle.

On the other hand, nitrites have side effects such as pulsating headache, nausea, vomiting, erythema and palpitation. Only a few of these present as clinical problems. The most serious is collapse or syncopal attacks due to marked hypotension. In the long history of nitrite use, however, the number of reports of such side effects is yet small.

An 81 year old patient with repeated episodes of collapse in response to sublingual administration of isosorbide dinitrate was treated. The case is reported with a review of the literature.

CASE REPORT

Patient. T. K. was an 81 year old female whose chief complaint was of precordial pain and attacks of unconsciousness. There was nothing relevant to the present illness in the past history or family history.

From around June 1973, the patient complained of pain which developed in the anterior chest and extended through to her left back. The pain had occurred on exertion. She was hospitalized in Yura Hospital from October 1973 to May 1974 with a diagnosis of angina pectoris. Soon after discharge, anginal attacks again occurred with gradual aggravation. She was admitted again near the end of June, 1974, but her anginal attacks increased in frequency. In 1976, angina pectoris unrelated to exercise developed and gradually increased in frequency to be present during the majority of her attacks. Towards the end of August 1977, the frequency of her attacks increased. Intense precordial pain and a sensation of strangulation in the chest occurred approximately once a day. Each of these attacks subsided within a few mimutes of sublingual administration of 1 tablet (10 mg) of isosorbide dinitrate (ID). The blood pressure at that time was 120–130 mmHg systolic and 60–70 mmHg diastolic. Occasionally she complained of a mild heavy sensation in her head following oral administration of ID. From the beginning of September 1977, sporadic ventricular extrasystoles appeared both at rest and during attacks.

Physical examination. Physical examination on September 26, 1977, showed body height 141.5 cm, weight 53 kg, thick subcutaneous fat, blood pressure 130/70 mmHg, pulse 65/min, regular, and of good character; slightly anemic palpebral conjunctiva. No cyanosis was noted in her lips, fingers or toes. No dilatation of the cervical veins was noted. Heart sounds were pure and without abnormal components in the I and II sounds. A mild IV sound was heard at the apex. The apex beat was not definitely palpable and no thrill was felt. The lung liver border was at the IVth rib. The abdomen was flat and neither liver nor spleen was palpable. No tenderness, local resistance or ascites was noted. Tendon reflexes were normal and no pathological reflexes were elicited.

Course before and after the syncopal attack. As shown in Fig. 1, from the last part of August 1977, the anginal attacks gradually worsened and 2–3 attacks occurred one day towards the end of September. She took ID sublingually at the time of each attack and obtained relief. On account of this, her appetite decreased from the beginning of September, with a gradual fall in water intake. At 5 a.m., September 29, she experienced mild precordial pain. This became

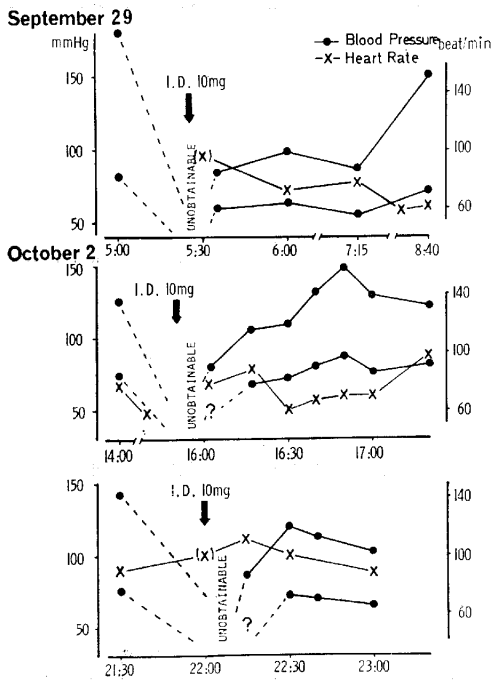

Fig. 1. Blood pressure and heart rate before, during, and after the attacks of collapse. Closed circles show the systolic and diastolic blood pressure, and crosses mark the heart rate. (×)=heart rate calculated from the electrocardiogram which was recorded during the attack. ID=isosorbide dinitrate.

worse immediately after her return from the toilet, and was accompanied by a sensation of strangulation and backache. The blood pressure was 170/82 mmHg at this time. She took 10 mg ID herself sublingually immediately but continued to feel a sensation of general weakness. She lapsed into a stupor and her pulse was hardly palpable at 5.35 a.m.. In response to a drip infusion of noradrenaline, the blood pressure returned to 86/60 mmHg at 5.45 a.m.. This was accompanied by recovery of consciousness, but the systolic blood pressure stayed below 90 mmHg for more than 1 hour. She experienced no anginal attacks thereafter, having a favorable course until 15.30, October 2, when she again felt discomfort in her chest, which was soon accompanied by anterior chest pain. At 15.50, 10 mg ID was administratered sublingually. Intense general malaise, weakness and a cold sweat developed 1-2 min later. At 15.55, the pulse became non-palpable, with mild cyanosis in the fingertips. After noradrenaline administration, a weak pulse became palpable at 16.00 and the blood pressure was 80 mmHg systolic by palpation. At 16.15, her blood pressure was 106/68 mmHg, heart rate 88/min, and a blood pressure of 130-150/70-90 mmHg and heart rate of

65-90/min continued thereafter. At 21.30, the blood pressure was 142/76 mmHg and heart rate 90/min. At 22.00, mild chest discomfort appeared and 10 mg ID was administered sublingually. At 22.05, yawning occurred frequently and general weakness, cold sweat, and cyanosis of the extremities were evident. The pulse was impalpable. After oxygen inhalation and an intravenous drip infusion of isoproterenol, the systolic blood pressure became 88 mmHg by palpation and heart rate 110/min at 22.15, and 120/72 mmHg and 110/min at 22.30 indicating recovery. Thereafter nitrite preparations such as ID were ceased despite mild anginal attacks. She recovered with oxygen inhalation and sedatives.

Laboratory results. At the time of admission, the urine and feces were free of abnormalities. The peripheral blood results were RBC 363×10^4, Hb 70%, Ht 33% and WBC 5000 with a normal differential count. Blood biochemical analysis showed GOT 20 Ku, GPT 9 Ku, LDH 236 u, Na 145 mEq/L, K 4.6 mEq/L, urea N 18 mg/dl, cholesterol 182 mg/dl, neutral fat 127 mg/dl, β-lipoprotein 3.2 mg/dl, phospholipid 278 mg/dl and fasting blood sugar 78 mg/dl, without any particular abnormalities. Approximately similar values continued thereafter until the syncopal attacks. Table 1 summarizes the results of tests over a period of several days after September 29. No abnormalities were found in these results on the morning of the 29th. On the 30th, GOT was 96 Ku and LDH 450 u, indicating a mild rise, suggesting development of a small necrotic lesion in the myocardium due to the attack on the 29th. The subsequent course, however, was uneventful and no enzyme changes suggestive of myocardial necrosis occurred after the attack on October 2.

TABLE 1. LABORATORY EXAMINATIONS

Examination	Date of examination						
	July 13	September 29	30	October 1	2	3	4
GOT (KU)	20	39	96	70	55	64	50
GPT (KU)	9	21		22	10	19	15
LDH (WU)		130	450	330	290	280	280
ESR (1h/2h)			50/96		50/78		
WBC (count/cm^3)	5000	7850	4900	5000	5000	5050	
Na (mEq/L)		142	134				
K (mEq/L)		4.7	4.2				
CRP	(−)				(+)	(+)	

ECG. Fig. 2 shows the ECG prior to the syncopal attack (September 26, 1977). The QT interval is prolonged (QT ratio = 1.30) and lead V_4-V_6 shows

ST depression and biphasic T waves. Such QT prolongation might be due in part to long term use of 90 mg prenylamine (4–6) daily. For this reason, prenylamine was ceased immediately. The left side of Fig. 3 is the ECG during the

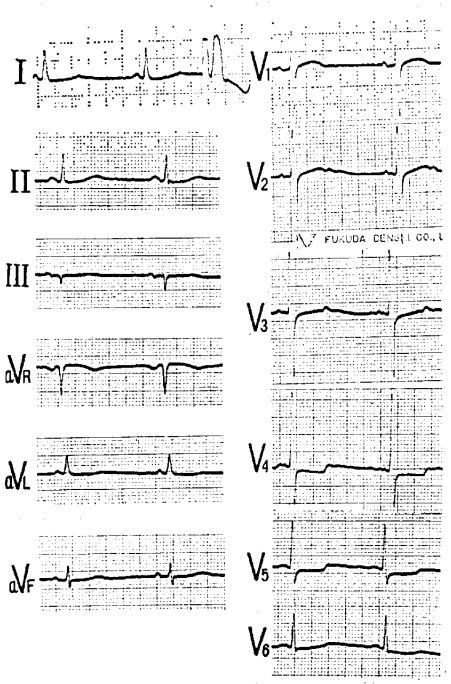

Fig. 2. Electrocardiogram on September 26, 1977.

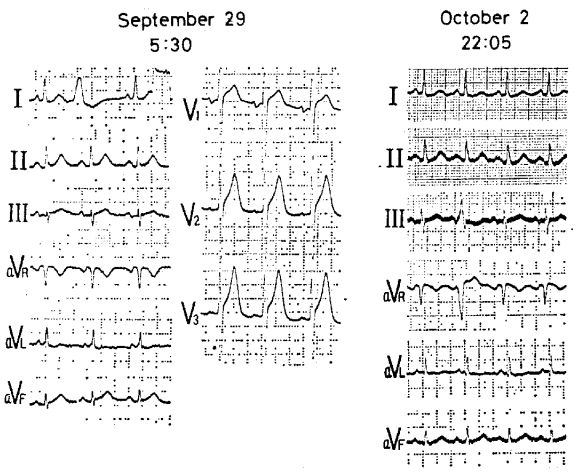

Fig. 3. Electrocardiograms during the attacks of collapse. Left; electrocardiogram during the first attack. Right; electrocardiogram during the third attack.

first syncopal attack (5.30 a.m. on the 29th) and the right side, that during the third attack (22.05 on the 2nd). While not all the leads were recorded on each of these occasions, ST elevation in II, aV_F and V_1-V_3 and increase in the height of the T wave in I, II, aV_F and V_1-V_3 occurred in the first attack. Similar changes probably occurred in the ECG during the third attack, though no precordial leads were recorded. This attack thus does not appear to represent Stokes-Adams syndrome due to arrhythmia.

Fig. 4 is the ECG taken on the morning of October 4. ST-T shows recovery almost to the level on September 26, with normalization of the QT ratio to 0.95.

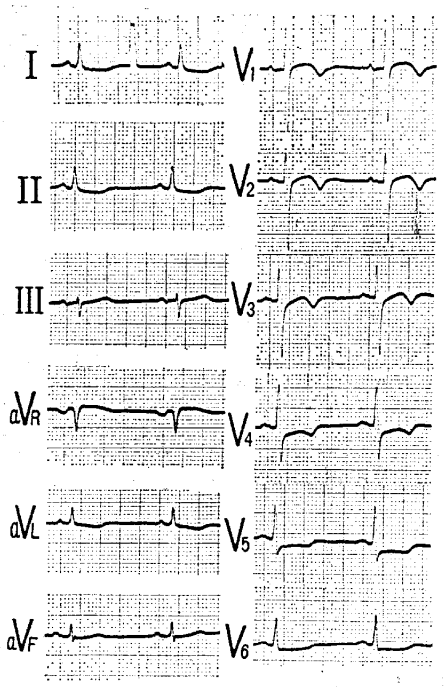

Fig. 4. Electrocardiogram on October 4, 1977. The patient was conscious and without complaints.

DISCUSSION

The specific effect of nitrites including nitroglycerin on anginal attacks has been known for a long time. At present, nitrite represents the only drug capable of causing a remission or interruption of the attack. While many mechanisms of action of nitrite preparations have been suggested, dilatation of peripheral blood vessels, especially the peripheral venous system to decrease both the venous return to the heart and the preload appears to be one of the most important mechanisms. In response to decrease in the stroke volume and the subsequent

TABLE 2. PREVIOUS REPORTS OF CASES OF CIRCULATORY COLLAPSE DUE TO NITROGLYCERIN

Authors	Case of circulatory collapse							
	Age	Sex	Dose of nitroglycerin	Blood pressure before/during attack		Heart rate during attack	Interval to attack	Clinical diagnosis
Hornert (22)	?	M	one drop	?	?	39	About 4h.	Malswallow
Loeb (23)	55	M	0.5mg	190/?	135/45	?	?	Hypertension
White & Sprague (24.25)	1. 52	M	0.65mg	155/95	?	Bradycardia	Several min.	AP
	2. 68	M	?	?	?	?	Several min.	AP
	3. 60	F	0.32mg	190/100	110/85	Bradycardia	10 min.	AP
Prodger & Ayman (26)	1. 67	F	1.3mg	158/78	Unobtainable	Bradycardia	10 min.	Hypertension & AP
	2. 58	F	0.65mg	172/84	82/52	Bradycardia	3.5 min.	Hypertension
	3. 64	F	1.3mg	178/98	90/66	Bradycardia	Within 9 min.	Hypertension
	4. 63	F	0.65mg	136/108	Unobtainable	Bradycardia	6 min.	Hypertension & AP
Lueth & Hanks (27)	1. 68	F	0.24mg	220/120	Unobtainable	?	2-3 min.	Hypertension
	2. 52	F	0.40mg	224/124	118/74	?	5 min.	Hypertension
	3. 57	F	0.40mg	176/106	134/112	Normal rate	3 min.	Hypertension
	4. 45	F	0.60mg	250/120	?	?	7 min.	Hypertension
	5. 47	M	0.60mg	150/90	?	?	7 min.	Hypertension
	6. 51	F	0.40mg	198/115	115/74	?	7 min.	Hypertension
	sublingual							
Come & Pitt (8)	1. 78	M	0.40mg	115/80	90/?	Bradycardia	5 min.	MI & AP
	2. 67	M	0.30mg	124 (mean)	59 (mean)	68	11 min.	MI
	intravenous							
	1. 77	M	17.6μg/min.	100 (mean)	53 (mean)	54	4 min.	Hypertension & MI
			5-7μg/min.	90 (mean)	64 (mean)	50	9 min.	
	2. 63	M	5-26.6μg/min.	76 (mean)	33 (mean)	47	10 min.	MI
	3. 45	M	5-56.5μg/min.	84 (mean)	38 (mean)	45	25 min.	MI
			10-36.5μg/min.	84 (mean)	62 (mean)	92	30 min.	

M=male, F=female, MI=myocardial infarction, AP=angina pectoris

fall of blood pressure, the heart rate usually increases via the reflex mediated by the sympathetic nervous system (7–10) to maintain the cardiac output. When no increase of heart rate occurs or bradycardia appears despite the fall of blood pressure, cardiac output is decreased and the patient may collapse. Table 2 summarizes the reports of collapse caused by nitrites collected from the literature. Many reports point out a relative or absolute bradycardia at the time of the attack. Come and Pitt (11) pointed out the effect of atropine on the bradycardia and collapse, and suggested decrease of the central venous blood volume (12), vagal excitation in response to the centripetal stimulation of the sympathetic nervous system (13) and vagal inhibition of the sympathetic nerve (14), as the causes for collapse. According to Karp *et al.* (15) loss of consciousness or EEG abnormality does not occur until the mean blood pressure falls as low as 25 mmHg. In our patient, the mean blood pressure during the first and third attacks of collapse was probably below 25 mmHg in view of the hardly palpable pulse, but the heart rate was 94 and 100/min in the ECG respectively, indicating rather a tachycardia. In other words, these attacks of collapse did not appear to be due to the inhibition of the sympathetic nervous system or excessive excitation of the vagus nerve. Hence the presence of factors not completely compensated by the ordinary compensatory mechanisms such as the reflex excitation of the sympathetic nervous system may be involved. Possible factors include a) decrease of cardiac output due to an inhibition of cardiac function (direct action on the myocardium), b) sudden decrease of peripheral resistance on account of dilatation of peripheral arteries and c) marked fall of venous return due to dilatation of peripheral veins, with an accompanying decrease in cardiac output. As to the direct action of the nitrites on the myocardium, a negative inotropic action has been reported by some, and a mild positive inotropic action by many others (16–18). The former action is said to be relatively mild. Direct action on the myocardium therefore was probably not the cause of collapse.

While the total body water is decreased in old age, the amount of extracellular fluid per body weight is said not to be different from that in younger patients (19). For this reason, the water reserve is small in the aged and dehydration and decrease of the circulatory blood volume readily occurs following any disturbance in water balance (20). In our patient, anorexia continued for about 1 month prior to the occurrence of the syncopal attack, probably causing a decrease in the circulatory blood volume. Administration of nitrite in such a state probably caused a marked fall of venous return, leading to the collapse attack. Nickerson (21) reported patients with hypersensitivity to nitrite. In our patient, no remarkable side effects were noted until the end of September 1977 despite the frequent use of ID, so that idiosyncracy does not appear to play a role. In an ECG obtained during two syncopal attacks, a marked myocardial ischemia was

suggested. The rapid course of these ECG changes and the lack of enzymatic abnormalities during the second and third syncopal attacks make it difficult to ascribe the attacks to myocardial ischemia. Myocardial ischemia due to a decrease of coronary blood flow induced by marked hypotension appears more reasonable.

When nitrites are used in the aged, therefore, the dose and their general state, especially the presence or absence of dehydration, should be studied well beforehand, along with careful observation of the blood pressure and heart rate before and after administration.

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