EFFECT OF EDTA2Na IN CONTRAST MEDIA ON HEMODYNAMIC AND ELECTROCARDIOGRAPHIC CHANGES DURING SELECTIVE CORONARY ANGIOGRAPHY

— An Experimental Study —

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CHANGES in ECG and cardiovascular dynamics after selective coronary angiography suggested that these effects might be due to the toxic effects of high sodium concentration, high osmolarity in the contrast media and transient hypoxia.¹⁻¹⁰

For coronary angiography, Urografin, Hypaque 75M and Renografin are often used. These contain 10–40 mg/dl of ethylenediamine tetraacetic acid disodium (EDTA2Na) as a stabilizer for the prevention of the liberation of iodine ions. As EDTA2Na chelates the Ca^{++} in the blood, it can be readily presumed that it will have some adverse effects on the cardiac contraction during selective coronary angiography. This paper describes the side effects observed during a detailed experimental study on EDTA2Na in the contrast media.

MATERIAL AND METHODS

1. EDTA2Na 20–100 mg/dl was added to the heparinized blood of normal persons at room temperatures and the Ca^{++} was measured by the orthocresolphthalein complexone method and pH was determined by the pH meter (Denmark Radiometer Co.).

2. Twenty-five adult mongrel dogs of 20–25 kg body weight were anesthetized with pentobarbital sodium administered intravenously. The trachea was cannulated for positive pressure ventilation. The chest cavity was then opened

through the fifth intercostal space and the pericardium was incised. After 2 mg/kg of heparin was administered, a Teflon tube was quickly inserted into the anterior descending branch of the left coronary artery. The blood perfusion of

Fig.1. Teflon tube was inserted into the LAD branch and connected to the femoral artery.

- SG 1: Strain gauge sutured in the LAD area.
SG 2: Strain gauge sutured in the LCF area.
ECG 1: Epicardial electrode attached in the LAD area.
ECG 2: Epicardial electrode attached in the LCF area.

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the anterior descending branch was obtained through the circuit which was connected to the right femoral artery.

A strain gauge and an epicardial electrode were sutured to the left ventricular myocardium in the area supplied by the left anterior descending coronary artery (LAD) and another set of strain gauge and electrode in the area supplied by the left circumflex coronary artery (LCF). A catheter tip manometer (PC-470 manufactured by Millar Co.) was inserted into the left ventricle through the left internal carotid artery. The cardiac output was measured with an electromagnetic flow probe attached to the root of the aorta (Fig. 1). Ten ml of blood was drawn through the femoral artery with a syringe pre-warmed to a temperature of 37°C. EDTA2Na was then added to the blood and this blood was injected into the LAD branch. This procedure was repeated at appropriate intervals. The EDTA2Na concentration in the injected blood was increased sequentially to 100 mg/dl with increments of 20 mg/dl. After the injection of the blood into the LAD branch through the three-way cock at a rate of about 3 ml/sec, the following parameters were recorded: (1) left ventricular pressure (LV pressure), (2) cardiac output, (3) maximum dp/dt/P, (4) regional contractile force in the LAD and LCF areas, (5) heart rate, QT interval and T wave.

3. Under the same conditions EDTA2Na and 2% CaCl₂ solution containing levels of Ca⁺⁺ equivalent were added to the blood, and following the injection of the mixture solution into the coronary artery, hemodynamic and electrocardiograph changes were observed.

RESULTS

1. The blood Ca⁺⁺ was 8–10 mg/dl, but it decreased to 6.7 mg/dl on the average at 20 mg/dl of EDTA2Na, 4.8 mg/dl at 40 mg/dl, 2.9 mg/dl at 60 mg/dl and 0.8 mg/dl at 80 mg/dl (Fig. 2-a). There was a mild reduction in pH, as shown in Fig. 2-b.

2. Figs. 3–6 illustrate the temporary hemodynamic changes in the blood with EDTA2Na. Illustrated are the left ventricular pressure, dp/dt/P, the force traces from two strain gauges in the LAD and LCF areas and the cardiac output: (1) there was only a mild reduction in the left ventricular systolic pressure at 20–80 mg/dl of EDTA2Na; (2) max. dp/dt/P and (3) cardiac output began to decrease at 40 mg/dl of EDTA2Na and the decrease became obvious

following the increase in the concentration of EDTA2Na; (4) immediately after the injection of blood containing EDTA2Na, there was a reduction in contractile force. Paradoxical systolic expansion occurred in the LAD area with EDTA2Na of more than 60 mg/dl, as evidenced by the negative force development (Fig. 5,6). Reduction in the contractile force varied depending on the level of EDTA2Na and returned to the control level 30–60 seconds after the injection. Contrarily, the force developed in the LCF area remained unchanged or rather increased (Fig. 3,4,5,6). (5) The pulse rate remained unchanged but the changes in the T wave and prolongation of the QT interval were observed in all the cases (Fig. 7, 8, 9, 10). There

Fig.2-a. Changes of blood Ca⁺⁺ with EDTA2Na.

Fig.2-b. Changes of blood pH with EDTA2Na.

Fig.3.

Fig.4.

Fig.5.

Fig.6.

Fig.3, 4, 5, 6. On the left are control tracings and hemodynamic changes following blood perfusion with 20, 40, 60, 80mg/dl EDTA2Na.

The contractile force in the LAD area decreases apparently with 40mg/dl EDTA2Na. The contractile force in the LCF area remains unchanged and rather increases with 80mg/dl EDTA2na. Left ventricular pressure, $dp/dt/P$, cardiac output reduce slightly.

Fig.7.

Fig.8.

Fig.9.

was a prolongation in corrected QT interval

($k = \frac{QT}{\sqrt{RR}}$): 4.5% at 20 mg/dl of EDTA2Na,

16.3% at 40 mg/dl, 18.2% at 60 mg/dl and 20.9% at 80 mg/dl (Fig. 11). The T wave of epicardial lead which was sutured in the LAD area became deeper depending on the level of

EDTA2Na. The T wave in lead II and epicardial lead in the LCF area showed changes of biphasic pattern. In addition, the ventricular premature beat usually increased and the electrical alternans of T wave accompanied by pulsus alternans in the left ventricular pressure trace were occasionally observed (Fig. 12).

Following the increase in the concentration of

Fig.10.

Fig.7, 8, 9, 10: On the left are control tracings of lead II, epicardial lead in the LAD area and epicardial lead in the LCF area. After the injection of blood with EDTA2Na, the T wave becomes more deep and wide. The QT interval prolongs. In this representative dog experiment, ventricular tachycardia occurred and resulted in ventricular fibrillation with 80mg/dl EDTA2Na.

Fig.11.

EDTA2Na, ventricular fibrillation appeared suddenly; it occurred in 16% of the experimental dogs at 60 mg/dl of EDTA2Na, in 68% at 80 mg/dl and in all the dogs at 100 mg/dl (Fig. 13).

3. After adding EDTA2Na and Ca^{++} in the amount equivalent to the EDTA2Na, the changes described above were not observed with EDTA2Na in doses up to 500 mg/dl (Fig. 14).

DISCUSSION

As EDTA2Na and Ca^{++} react with each other in the molar ratio of 1;1, 1 mg of Ca^{++} binds 9.3 mg of EDTA2Na. The decrease of the blood Ca^{++} is proportional to the concentration of EDTA2Na administered: the Ca^{++} in the blood is decreased to about half of the normal value with 40 mg/dl of EDTA2Na and almost all of the Ca^{++} were chelated with 80 mg/dl EDTA2Na. There is only a mild reduction in pH. Following the increase in the concentration of EDTA2Na, the Na^+ also increases, but 100 mg/dl of EDTA2Na contains only 6 mEq/L of Na^+ . Therefore the effect of Na^+ contained in the added EDTA2Na can be ignored.

Upon injecting blood containing EDTA2Na into the LAD branch the reduction in the force observed in the LAD area. It was parallel to the level of Ca^{++} , and with EDTA2Na at more than 60–80 mg/dl, paradoxical systolic expansion occurred in the LAD area, as evidenced by the negative force development. It was evident that there was little change in the overall pattern of contraction in the LCF area. Decrease in the left ventricular pressure, cardiac output and max. dp/dt/P was slight and would be due to the compensation of the surrounding myocardium, which was suggested by the increase in the contraction of LCF area. The electrical alternans

Fig.12. In another representative dog experiment, the left ventricular pressure, the force traces from the two strain gauges and ECG are illustrated following the injection of blood with 40mg/dl EDTA2Na. The electrical alternans of T wave is appeared and associated with the pulsus alternans. Note the attenuation of some contractions in the LAD area, with a minimal effect on contraction in the LCF area.

Fig.13. Frequency of ventricular fibrillation.

of T wave accompanied by pulsus alternans appeared in the epicardial lead of the LAD area and in the left ventricular pressure tracings in some cases (Fig. 12). The attenuation of some

contractions in the LAD area was apparent and was associated with pulsus alternans. It is a phenomenon due to the electromechanical dissociation caused by inadequate amounts of Ca^{++} reaching the myofilaments.¹¹⁻¹³

When the Ca^{++} in the cell membrane is removed by means of a chelating agent or under perfusion with a low Ca^{++} solution, it is known that the plateau of the intracellular action potential is prolonged.^{14,15} Prolongation of the QT interval observed in this experiment could be caused by a similar mechanism. The prolongation of the QT interval was accompanied by the increase of ventricular premature beats, and when almost all of the Ca^{++} in the blood are chelated by EDTA2Na, ventricular fibrillation occurs suddenly. It may be caused by the electrical unevenness due to the difference in the excitation between the myocardial cell group in the LAD area and the cell groups in the other areas. It is presumed that the prolongation of the plateau phase of the intracellular action potential occurs only in some cell groups, and an electric current flows between the groups and other cell groups which are normally depolarized

Fig.14. In spite of the large dose of EDTA2Na such as 500mg/dl, the contractile force in the LAD area, left ventricular pressure and ECG remained unchanged in the presence of equivalent Ca^{++} .

and when local re-entry begins ventricular fibrillation occurs.

Even with large doses of EDTA2Na, the above mentioned changes did not occur in the presence of an equivalent amount of Ca^{++} , and so it is evident that they are due to the decrease of Ca^{++} . (Fig. 14)

From the experimental results it is revealed that EDTA2Na contributes to ventricular arrhythmia, changes in the T wave and reduction in cardiac performance, besides the various toxic features of contrast medium which have been previously reported. It is also suggested that the safety range of EDTA2Na is very narrow.

EDTA2Na is now an indispensable substance in preventing the liberation of free iodine from the contrast media during long-term preservation, but the dose to be used should be re-examined in regard to its effect as a stabilizer and to its side effects.

SUMMARY

The contrast media used contains 10–40 mg/dl of EDTA2Na as a stabilizer, and its effect on cardiac contraction during selective coronary

angiography was studied experimentally.

When EDTA2Na was added to the blood, the Ca^{++} in the blood was reduced to about half at 40 mg/dl and Ca^{++} was almost completely chelated at levels of more than 80 mg/dl. EDTA2Na was added to 10 ml of blood at varying concentrations and injected into the LAD artery of laboratory dogs, and the changes related to the concentration were observed in regard to the left ventricular pressure, max.dp/dt/P , cardiac output, contraction in the LAD area and the LCF area, and ECG. There was observed no marked reduction in the left ventricular pressure and cardiac output but the reduction in the contraction in the LAD area was marked. When the concentration was over 60 mg/dl, paradoxical systolic expansion began to appear. Depending on the concentration of EDTA2Na, the QT interval was prolonged and the ventricular extra systole increased in frequency; ventricular fibrillation occurred in 16% of the dogs at 60 mg/dl, in 68% at 80 mg/dl and in all the dogs at 100 mg/dl.

This study demonstrates that the administration of EDTA2Na produces significant transient

changes in ECG and cardiovascular function and that it is one of the factors involved in these changes observed during selective coronary angiography with angiographic agents containing EDTA2Na.

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