The Electrocardiographic Effects of Hypocalcemia Induced in Normal Subjects with Edathamil Disodium

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In the past, it has not been possible to study the electrocardiographic effects of hypocalcemia in normal subjects. Edathamil disodium is a powerful chelating agent with a strong affinity for ionic calcium when given intravenously. This agent was used to produce hypocalcemia in normal subjects so that electrocardiographic effects could be studied. The major changes produced in the electrocardiogram with the induction of hypocalcemia were shortening of the R-R interval, prolongation of the RS-T and Q-T intervals, all of which were proportional to the degree of hypocalcemia. No change in the spatial P, QRS and T vectors, no T wave flattening or inversion and no elevation or depression of the RS-T segment appeared with hypocalcemia.

In the past, it has been necessary to study the effects of hypocalcemia in the presence of disease. Since many factors in ill patients tend to influence the electrocardiogram, it has been difficult to be certain which changes in such patients were due only to hypocalcemia. The disadvantages of such electrocardiographic studies are obvious.

Since edathamil disodium is a complexing agent which has a strong affinity for calcium and will reduce serum ionized calcium when injected intravenously, it was felt that this agent would prove useful in defining electrocardiographic changes secondary to relatively uncomplicated hypocalcemia in normal persons. Carter and Andrus' first reported Q-T prolongation in hypocalcemia tetany in 1922. Since then numerous studies of the electrocardiographic changes occurring with hypocalcemia in various disease states have been reported. 5-10 Many early investigators utilized only one or two electrocardiographic leads in reporting RS-T segment, Q-T interval and T-wave changes. Often other serum electrolytes were present in abnormal concentrations or were not determined, and these studies have led to many conflicting reports. In more recent years, however, several investigators have attempted to clarify this subject by utilizing more leads, 9-11 correcting values of the Q-T intervals for rate, 4, 9-11 and using better methods for the measurement of intervals. 11-13 The present authors are aware of no prior studies concerning the electrolyte and electrocardiographic changes during hypocalcemia in otherwise normal subjects.

Method

Seven subjects, all of whom were considered to be free of organic disease, were selected for study. In five of these subjects an intravenous infusion of edathamil disodium (3 Gm. in 400 ml. of solution at a pH of 7.4 to 7.8) was begun at zero time. In the remaining two subjects an intravenous infusion of edathamil calcium-disodium (3 Gm. in 400 ml. of solution at a pH of 7.4) was begun.  

* Each gram of edathamil disodium (Na₂ EDTA) can chelate 108 mg. of calcium at a pH of 7.4, and in this combination the calcium is not ionized. At this pH edathamil disodium is actually a mixture of the disodium and trisodium salts, but for convenience will be termed edathamil disodium (Na₂ EDTA).

Edathamil calcium-disodium (Ca Na₂ EDTA) combines with no additional calcium. This makes it a useful preparation to use as a control to insure that the changes seen were due to hypocalcemia and not to the ethylene-diaminetetraacetate portion of the molecule or to the associated sodium and potassium changes which are similar after the injection of either substance.
was completed at an average time of 20.4 minutes (15 to 27 minutes). The vehicle (400 ml. of solution) was 5 per cent glucose in subjects 1 and 2; all others received normal saline. Blood samples for plasma sodium, potassium, calcium, and phosphate determinations were withdrawn at frequent intervals for the first two hours, then hourly for four to six hours. Electrocardiograms were recorded before the infusion and at the time blood specimens were withdrawn.

Electrocardiograms were recorded with a Sanborn direct-writing electrocardiograph at standard speed (25 mm. per second) and a Sanborn twin-beam photographic electrocardiograph at triple standard speed (75 mm. per second). The 12 standard leads were taken with the direct-writing instrument and selected leads for study were obtained with the twin-beam photographic instrument.

**Electrocardiographic Measurements.** In the limb leads, measurements were carried out in that lead in which QRS and T complexes were of greatest magnitude. In all cases studied this was lead II. In the precordial leads, measurements were carried out in the first lead lateral to the zone of QRS transition which showed large R waves, usually V3 or V4. Standardization for amplitude was checked in each lead, and suitable correction was made when necessary. The various intervals were measured by the technic of Lepeschkin and Surawicz with the following modifications: (1) both the initiation and termination of the T wave were measured by the tangential method and (2) the points at which tangents drawn to the ascending and descending limbs of the T wave intersected a line drawn parallel to the baseline through the S-T junction were considered as the beginning and end of the T wave. The intervals measured were as follows: (1) beginning of QRS to the end of T (Q-T), (2) beginning of QRS to the beginning of T (Q-oT), (3) beginning of QRS to apex of T (Q-aT), (4) beginning of T to the end of T (T), (e) beginning of QRS to end of U (Q-U) and (5) the P-R, QRS, and R-R intervals by standard definition. The Q-T, Q-oT, and T intervals were corrected, as outlined by Lepeschkin and Surawicz, using the formula of Bazett.

**RESULTS**

**Electrolyte Changes.** In terms of change from control levels expressed in milliequivalents per liter, the most pronounced variations after edathamil disodium (Na2 EDTA) administration occurred in plasma calcium and plasma sodium (fig. 1). The electrolyte changes produced by edathamil calcium-disodium (Ca Na2 EDTA) (the calcium salt) were insignificant, except possibly in the case of potassium.

With the administration of Na2 EDTA, plasma calcium values dropped from 1.0 to 1.7 mEq. per liter below their control values with the lowest point at the end or shortly after the completion of the infusion. This represents a mean percentile change of 31.4. Return toward normal was gradual, usually beginning within 15 minutes after completion of the infusion.

In all cases, plasma potassium fell below the control value by 0.1 to 0.5 mEq. per liter. There was no apparent correlation between the degree of depression of plasma calcium and that of plasma potassium. It is unlikely that the fall in potassium is directly related to the induction of hypocalcemia by Na2 EDTA since it occurs following the administration of Ca Na2 EDTA as well.

Phosphate levels showed a more gradual fall and a more prolonged depression with a tendency to show a late rise above the control value. The absolute change was between 0.3 to 0.5 mEq. per liter below the control value. These same changes have been noted in patients similarly treated except that normal saline was substituted for edathamil solutions, so this effect is probably independent of edathamil.

There was some variable rise in sodium values (1.0 to 8.0 mEq. per liter, or a mean percentile change of 2.9 per cent), probably related to the nature of the chelating salt and the vehicle used. In general, this rise reached its peak during the infusion or within 30 minutes following. No changes have been recognized in the electrocardiogram due to changes in the sodium ion concentration. The change produced in the plasma sodium concentration of these subjects is small and is present in the control subjects; thus, it is felt that the electrocardiographic changes described in this study are entirely related to the changes in the calcium ion concentration.

Reynolds also reported no changes in the electrocardiogram with variation in magnesium ion concentration. Another investigator failed to demonstrate significant changes in serum levels of magnesium, calcium, pH, sodium and copper, following the administration of Ca Na2 EDTA. Plasma magnesium and blood pH determinations were not done in the present study.
FIG. 1. The change from control values of plasma calcium, phosphate, potassium and sodium during and following the intravenous administration of edathamil disodium (Na₂EDTA).

FIG. 2. The change from control values of P-R, QRS, and R-R intervals during and following the intravenous administration of edathamil disodium (Na₂EDTA).

FIG. 3. The change from control values of Q-T, Q-oT, and T intervals during and following the intravenous administration of edathamil disodium (Na₂EDTA).

FIG. 4. The change from control values of plasma calcium, phosphate, potassium and sodium during and following the intravenous administration of edathamil calcium-disodium (Ca Na₂ EDTA).

FIG. 5. The change from control values of R-R, P-R, and QRS intervals during and following the intravenous administration of edathamil calcium-disodium (Ca Na₂ EDTA).

FIG. 6. The change from control values of the Q-T, Q-oT and T intervals during and following the intravenous administration of edathamil calcium-disodium (Ca Na₂ EDTA).
**Subjective Changes.** No symptoms appeared during the infusion of Ca Na$_2$ EDTA. All five subjects who received Na$_2$ EDTA developed mild symptoms, usually beginning within two or three minutes after starting the intravenous infusion. Aching, cramping pain developed along the course of the vein through which the infusion was given. This was apparently of muscular origin and was readily alleviated by light local massage, but immediately reappeared as massage was stopped. A fine, generalized muscular tremor appeared during the infusion in all cases but lasted only two to five minutes. Numbness and tingling were present in the hands, lips, and occasionally the feet. All subjective symptoms subsided with completion of the infusion or within 10 minutes following infusion.

**Changes in the Amplitude and Contour of the Electrocardiogram.** During the infusion of Na$_2$ EDTA there was a general trend for the P, QRS and T complexes to become slightly reduced in amplitude. These changes were very small and generally less than 1 mm. (standardization of 10 mm. equals 1 mv.). No RS-T segment shift occurred with the edathamil disodium, but in one of the two subjects receiving Ca Na$_2$ EDTA there was an unexplained decrease in the amplitude of the QRS (over 2 mm.) and T (1.8 mm.) with S-T segment depression (0.5 mm.) at 240 minutes only. No other changes were noted with the infusion of Ca Na$_2$ EDTA.

Spatial vector analysis revealed no significant changes in the electric axis of the various electrocardiographic waves. It is felt, therefore, that these changes in amplitude are not due to a change in the electric axis of the P, QRS, T or S-T segment.

<table>
<thead>
<tr>
<th>Interval</th>
<th>Correlation Coefficient</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-R</td>
<td>+0.78</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Q-oT</td>
<td>-0.69</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Q-T</td>
<td>-0.76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T</td>
<td>-0.21</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

No dramatic changes were seen in the contour of the electrocardiogram. No inversion of T waves was encountered. In some instances there was a tendency for the beginning of the T wave to become blended into the RS-T segment. This was particularly true if there was slight S-T segment elevation present in the control precordial leads. The effect of this change was to make exact measurement of the beginning of the T wave very difficult, thus making the accurate measurement of Q-oT problematic. Since measurement of the interval Q-oT (length of the S-T segment) and the beginning of the T wave cannot be accurately determined in all cases, one cannot be certain that the RS-T segment is the interval primarily lengthened by hypocalcemia. Indeed, in this study, statistical analysis fails to reveal that the Q-oT is lengthened significantly more than the Q-T as the serum calcium falls ($p > 0.1$).

**Changes in the Intervals of the Electrocardiogram.** Prolongation of the Q-T and the Q-oT intervals has been observed by many previous investigators in the presence of hypocalcemia, but changes in the R-R interval have not been reported to occur. In this study marked changes occurred in the R-R, the Q-T, and the Q-oT intervals. The R-R interval was shortened (fig. 2); the Q-T, and the Q-oT intervals were prolonged (fig. 3). The reduction in R-R interval and the prolongation of Q-T and Q-oT intervals were proportional to the degree of hypocalcemia. In contrast, in the two subjects receiving edathamil calcium-disodium, there was no change in one and a prolongation in the R-R interval of the other (figs. 5 and 6).

These changes are statistically significant, and the close correlation of the degree of the changes in intervals with the absolute fall in serum calcium makes other factors, such as anxiety, much less probable causes of the effects seen (table 1).

The P-R interval showed no consistent nor appreciable change.

The QRS interval was consistently shortened during the period of infusion, but this was not correlated with the degree of hypocalcemia nor was it great enough to be of
definite significance (less than 0.01 second change).

The difficulties in measurement of the Q-T intervals and the misinterpretation of the Q-U interval for the Q-T interval have been emphasized by several authors who have suggested the use of multiple leads as utilized in this study as an aid in preventing this error. In the present study attempts in measurement of the Q-U interval were not always successful, since the shortened R-R interval caused the U wave (which was present, though small, in all control tracings) to be superimposed upon the following P wave, thus making measurements inaccurate. In those subjects in which the Q-U interval could be measured the change was generally less than 0.04 second prolongation.

SUMMARY

1. The electrocardiographic effects of hypocalcemia produced by intravenously administered edathamil disodium have been studied in normal subjects.

2. The major changes noted with the production of hypocalcemia have been: shortening of the R-R interval and prolongation of the Q-oT and Q-T intervals, all proportional to the degree of hypocalcemia.

3. Other changes noted to occur, but minor in degree or not well correlated with the fall in serum calcium, were: slight reduction in amplitude of the P, QRS, and T; merging of the RS-T segment and the ascending limb of the T wave; shortening of the QRS interval; and Q-U and T interval prolongation.

4. No change in spatial P, QRS, and T vectors occurred with hypocalcemia.

5. No T wave flattening or T wave inversion, and no elevation or depression of the RS-T segment appeared.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Dr. T. B. Schwartz for his helpful criticism and his assistance with the statistical analyses.

SUMMARIO IN INTERLINGUA

In le passato il non esseva possibile studiar le effectos electrocardiographic de hypocalcemia in subjectos normal. Edathamil-dinatrium es un potente agente chelative con un forte affinitate pro calcium ionic quando illo es administrate intravenosemente. Iste agente eseva usate pro producer hypocalcemia in subjectos normal de maniera que studiar le effectos electrocardiographic deveniva possibile. Le major alterationes producite in le electrocardiogramma per le induction de hypocalcemia eseva reduction del intervallo R-R e prolongation del intervallos RS-T e Q-T, omnes proportional al grado de hypocalcemia. Nulle alteration del spatial vectores P, QRS, e T, nulle applatattion o inversion del unda T, e nulle elevation o depression del segmento RS-T se manifestava in association con hypocalcemia.

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Circulation. 1956;13:837-842
doi: 10.1161/01.CIR.13.6.837

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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