Use of a Calcium Chelating Agent (NaEDTA) in Cardiac Arrhythmias

By Burton D. Cohen, M.D., Norton Spritz, M.D., Glenn D. Lubash, M.D., and Albert L. Rubin, M.D.

The interrelated effects of digitalis and various cations on cardiac rhythmicity are the subject of much recent interest. This paper presents additional data on this subject that carry important therapeutic implications. The chelating agent, disodium ethylene diamine tetra acetate (NaEDTA), has been used intravenously in 14 instances of supraventricular and ventricular arrhythmia. Digitalis had been administered previously in 13 instances, and various degrees of digitalization were encountered. This report summarizes our experience with NaEDTA as a test of the degree of digitalis therapy and as treatment of the arrhythmias observed.

It has been demonstrated that calcium and digitalis act synergistically on both myocardial contractility and irritability.1-6 Nalbandian et al.7, 8 have used this relationship practically and have developed an intravenous calcium tolerance test to quantitate the degree of digitalization. With this and other provocative tests, however, the end point may be a fatal arrhythmia.

Calcium binding, on the other hand, can be induced in vivo through the intravenous use of the chelating agent, disodium ethylene diamine tetra acetate (NaEDTA) without significantly altering plasma potassium or magnesium.9, 10 Experiments in animals10, 11 and in man12, 13 have shown that reduction in calcium ions so induced can affect arrhythmias resulting from digitalis therapy. Since reversal of arrhythmia is a positive end point, we have used rapidly injected intravenous NaEDTA* in patients with arrhythmias, most often in the setting of previous digitalis administration.

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Materials and Methods

Thirteen patients with cardiac arrhythmias were chosen for study. All but one had received digitalis. They were treated on 14 occasions with intravenous injections of NaEDTA diluted with 5 per cent dextrose in water to a concentration of 20 mg. per ml., given at rates of 5 to 25 ml. (100 to 500 mg.) per minute. During the procedure a continuous electrocardiogram was taken on a direct-writing machine. One of the standard 12 electrocardiographic leads was employed in most cases. In one patient esophageal leads were obtained and in another a bipolar atrial lead using the second and fourth interspace to the right of the sternum (designated Lewis lead) was used.

FIG. 1. Electrocardiograms in patient M.M. showing atrial tachycardia with A-V block and ventricular premature contractions (9:00 p.m.) NaEDTA produced no change in the arrhythmia (9:10 p.m.). Following potassium chloride intravenously the electrocardiogram reverted to normal sinus rhythm with Wenckebach phenomenon (leads II and V1 at 9:00 a.m.). The latter persisted for 16 days and was followed by an episode of nodal rhythm and, finally, normal sinus rhythm without A-V block.
Fig. 2 Top. Electrocardiograms in patient H.B. showing atrial tachycardia with A-V block (2:00 p.m.) not responding to NaEDTA (2:10 p.m.). Six hours after further digitalis therapy, the electrocardiogram reverted to normal sinus rhythm (8:15 p.m.). Twelve hours later, atrial tachycardia recurred (8:00 a.m.), but again reverted to normal sinus rhythm 6 hours after additional digitoxin. Digitalis was continued without further incident.

Fig. 3 Bottom. Electrocardiograms in patient J.M. showing atrial flutter (7:00 p.m.) confirmed by esophageal lead. After NaEDTA produced no change in the arrhythmia (7:10 p.m.), the patient was given potassium chloride intravenously with reversion to normal sinus rhythm (8:00 a.m.). Thereafter he received 0.1 mg. of digitoxin daily without incident.
employed. Blood samples from veins other than those used for NaEDTA injection were obtained before and after the test.

Plasma potassium was determined with a flame photometer with use of a lithium internal standard. Serum calcium was determined by the method of Sobel and Hanok modified for semimicrotechnic; this procedure measures divalent ions and includes magnesium.

RESULTS

Supraventricular Arrhythmias. NaEDTA was administered to 6 patients with supraventricular arrhythmias. In all instances the arrhythmia was unchanged. The data are presented in table 1.

All the patients had received digitalis therapy and in 2 of these, the arrhythmia, atrial tachycardia with block, was thought to be the result of this therapy. In these patients, M.M. (fig. 1) and A.R., this rhythm was unchanged by NaEDTA therapy and reverted to normal sinus rhythm after the administration of potassium chloride. Patient H.B. also showed atrial tachycardia with block. Further digitalis therapy was associated with conversion of the arrhythmia to a sinus mechanism (fig. 2), indicating that digitalis intoxication was probably not a factor in its production.

Patient J.M., who had atrial flutter that did not change after NaEDTA therapy, reverted to normal sinus rhythm after administration of potassium chloride (fig. 3). Since it has been shown that potassium chloride may be effective in the treatment of atrial flutter and since atrial flutter is uncommon as a manifestation of digitalis intoxication, this arrhythmia was not considered due to digitalis.

Patient P.G. had atrial flutter and had received inadequate digitalis therapy. NaEDTA injection caused no change, and the rhythm subsequently converted to atrial fibrillation after more digitalis was administered. The final patient in this group, L.M., developed first-degree heart block after receiving 1.4 mg. of digitoxin in 24 hours. NaEDTA injection caused no change. First-degree heart block persisted during the time the patient was given maintenance digitalis therapy.

Ventricular Arrhythmias. NaEDTA was administered 8 times to 7 patients with ventricular arrhythmias (table 2). All but 1 patient had received digitalis and in 6 instances, this therapy was considered responsible for the arrhythmia. In 5 of these 6, ventricular tachycardia reverted to normal sinus rhythm during the administration of 0.5 Gm. or less of NaEDTA (figs. 4 and 5).

One patient (M.Z.) received NaEDTA on 2 occasions. On the first trial, NaEDTA administration was associated with correction of ventricular bigeminy although digitalis therapy was obviously inadequate at that time. On the second, ventricular bigeminy did not respond to NaEDTA administration.
Table 1.—Results in Patients with Supraventricular Arrhythmias

<table>
<thead>
<tr>
<th>Patient, age, sex</th>
<th>Previous digitalis therapy</th>
<th>Electrocardiogram before test</th>
<th>Dose of NaEDTA Electrocardiogram after test</th>
<th>(mEq./L. including magnesium) Serum calcium</th>
<th>Plasma K immediately after KCl therapy (iv)</th>
<th>Plasma K immediately after KCl therapy</th>
<th>Subsequent digitalis therapy</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.M., 76, F</td>
<td>1.2 mg. digitoxin, then 0.1 and 0.2 on alternate days for 6 weeks</td>
<td>Atrial tachycardia with block</td>
<td>1.0 Gm. in 10 min.</td>
<td>No change</td>
<td>6.55</td>
<td>5.50</td>
<td>3.3</td>
<td>40 mEq. in 12 hours</td>
</tr>
<tr>
<td>AR, 80, F</td>
<td>0.1 mg. digitoxin every 2 days for 4 years, then 1.2 mg. in 72 hours, followed by 0.1 and 0.2 for 3 days</td>
<td>Atrial tachycardia with block</td>
<td>1.2 Gm. in 12 min.</td>
<td>No change</td>
<td>6.65</td>
<td>5.50</td>
<td>3.9</td>
<td>65 mEq. in 12 hours</td>
</tr>
<tr>
<td>HB, 83, F</td>
<td>1.4 mg. digitoxin in 12 hours</td>
<td>Atrial tachycardia with block</td>
<td>1.0 Gm. in 10 min.</td>
<td>No change</td>
<td>—</td>
<td>—</td>
<td>4.3</td>
<td>None</td>
</tr>
<tr>
<td>JM, 73, M</td>
<td>0.1 and 0.2 mg. digitoxin on alternate days for 4 months</td>
<td>Atrial flutter</td>
<td>1.0 Gm. in 10 min.</td>
<td>No change</td>
<td>5.70</td>
<td>2.30</td>
<td>3.5</td>
<td>100 mEq. in 12 hours</td>
</tr>
<tr>
<td>PG, 71, M</td>
<td>0.1 and 0.2 mg. digitoxin on alternate days for several years, then none for 2 weeks</td>
<td>Atrial flutter</td>
<td>1.5 Gm. in 15 min.</td>
<td>No change</td>
<td>5.22</td>
<td>4.42</td>
<td>5.4</td>
<td>None</td>
</tr>
<tr>
<td>LM, 69, F</td>
<td>1.4 mg. digitoxin in 24 hours</td>
<td>Normal sinus rhythm with 1st degree A-V block</td>
<td>1.0 Gm. in 10 min.</td>
<td>No change</td>
<td>6.95</td>
<td>5.90</td>
<td>4.4</td>
<td>None</td>
</tr>
</tbody>
</table>

HCVD, hypertensive cardiovascular disease; ASHD, arteriosclerotic heart disease; RHD, rheumatic heart disease.
Table 2.—Results in Patients with Ventricular Arrhythmias

<table>
<thead>
<tr>
<th>Patient age, sex</th>
<th>Previous digitalis therapy</th>
<th>Electrocardiogram before test</th>
<th>Dose of NaEDTA</th>
<th>Electrocardiogram after test</th>
<th>Subsequent KCl therapy (iv)</th>
<th>Plasma K before test</th>
<th>Plasma K immediately after KCl therapy</th>
<th>Subsequent digitalis therapy</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.B., 83, M ASHD</td>
<td>1.2 mg. digitoxin, then 0.1 and 0.2 alternately for 16 days</td>
<td>Ventricular tachycardia</td>
<td>0.5 Gm. in 1 min.</td>
<td>Normal sinus rhythm with 1st degree heart block</td>
<td>None</td>
<td>7.02</td>
<td>6.34</td>
<td>5.6</td>
<td>None</td>
</tr>
<tr>
<td>A.B., 79, F HCV</td>
<td>1.2 mg. digitoxin, then 0.1 and 0.2 alternately for 10 days</td>
<td>Ventricular tachycardia</td>
<td>0.2 Gm. in 2 min.</td>
<td>Normal sinus rhythm</td>
<td>None</td>
<td>5.20</td>
<td>4.43</td>
<td>3.7</td>
<td>40 mEq. in 1 hour</td>
</tr>
<tr>
<td>E.J., 62, F Cor pulmonale, sarcoid</td>
<td>0.1 Gm. digitalis lost for 2 weeks, then 1.0 Gm. daily for 3 days</td>
<td>Ventricular tachycardia</td>
<td>0.4 Gm. in 4 min.</td>
<td>Normal sinus rhythm</td>
<td>None</td>
<td>7.38</td>
<td>6.80</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>D.P., 50, F RHD</td>
<td>0.1 and 0.2 mg. digitoxin on alternate days for several years, then 0.5 in 12 hours</td>
<td>Ventricular tachycardia</td>
<td>0.5 Gm. in 1 min.</td>
<td>Atrial fibrillation</td>
<td>None</td>
<td>7.18</td>
<td>6.10</td>
<td>3.6</td>
<td>None</td>
</tr>
<tr>
<td>E.C., 55, F ASHD</td>
<td>0.6 mg. ouabain and 1.4 mg. digitoxin in 72 hours, 0.1 and 0.2 alternately for 7 days, then an additional 0.2 mg. ouabain in 2 hours</td>
<td>Ventricular tachycardia</td>
<td>0.4 Gm. in 4 min.</td>
<td>Sinus tachycardia with A-V dissociation</td>
<td>—</td>
<td>—</td>
<td>4.9</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>M.Z., 69, M ASHD</td>
<td>0.2 mg. digitoxin daily for 2 years, then 0.2 every 3 days for 1 month</td>
<td>Atrial fibrillation with frequent ventricular premature contractions, bigeminy</td>
<td>0.9 Gm. in 9 min.</td>
<td>Atrial fibrillation with rare ventricular premature contractions</td>
<td>None</td>
<td>6.02</td>
<td>5.70</td>
<td>4.4</td>
<td>None</td>
</tr>
<tr>
<td>Same patient</td>
<td>See preceding</td>
<td>Same rhythm as pretreatment EKG above</td>
<td>1.0 Gm. in 10 min.</td>
<td>No change</td>
<td>None</td>
<td>5.80</td>
<td>5.50</td>
<td>4.2</td>
<td>None</td>
</tr>
<tr>
<td>J.D., 81, M Cor pulmonale</td>
<td>None</td>
<td>Ventricular tachycardia</td>
<td>1.2 Gm. in 4 min.</td>
<td>No change</td>
<td>None</td>
<td>—</td>
<td>3.4</td>
<td>None</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: NaEDTA = Sodium EDTA; KCl = Potassium chloride.
although digitalis intoxication was suspected. This paradoxical response is presented in detail:

M.Z., a 69-year-old man, had normal sinus rhythm with marked first-degree heart block (P-R interval of 0.52 second) in 1949. In 1956 he developed congestive heart failure and was treated with 0.2 mg. of digitoxin daily without an initial digitalizing dose. Eighteen months later, he was hospitalized for amputation of a gangrenous toe. Since the duration of first-degree heart block was not known, digitalis was withheld. One week later, an electrocardiogram revealed atrial fibrillation with a ventricular rate of 50 per minute. Digitoxin was reinstituted at a dose of 0.1 mg. daily, to be administered only if radial pulse rates were more rapid than 60 per minute. On this schedule he received 0.1 mg. of digitoxin 2 to 3 times weekly.

During the first month of hospitalization, he had a weight gain of 9.9 Kg. and peripheral edema was noted, whereupon the dose of digitoxin was increased to 0.1 mg. daily. Over the next 3 days he was given mercurial injections without change in weight and then, 10.0 Gm. of ammonium chloride daily were administered by mouth. Electrocardiogram showed atrial fibrillation with a slow ventricular rate and premature ventricular contractions giving rise to bigeminy (fig. 6). A contin-
uous electrocardiogram during an injection of NaEDTA showed no change in the coupled rhythm over a 9-minute period until 0.9 Gm. had been administered. The bigeminy then disappeared and only occasional premature ventricular contractions were noted. Twelve hours later, however, he developed pulmonary edema without electrocardiographic change except for a slight increase in ventricular rate. During the succeeding 72 hours, 0.3 mg. of ouabain and 1.2 mg. of digitoxin were administered, following which ventricular bigeminy recurred. An additional 1.0 Gm. of NaEDTA administered in a 10-minute period produced no change in the arrhythmia. Following an injection of mercurial diuretic, his weight fell 2.8 Kg. in 18 hours. Electrocardiogram showed no further premature contraction and digitoxin was reinstituted at a dose of 0.1 and 0.2 mg. on alternate days without further incident.

A final patient, J.D., who had never received digitalis had ventricular tachycardia which did not respond to an injection of 1.2 Gm. of NaEDTA (fig. 7).

Toxicity. Toxicity to NaEDTA was not observed. In one instance (D.P.) ventricular tachycardia reverted to atrial fibrillation with a more rapid ventricular rate than that observed prior to the onset of the digitalis-induced ventricular tachycardia. Similarly in patient M.Z., the pulmonary edema that followed the first administration of NaEDTA may have been related to this therapy. It is suggested that the change in serum calcium may have led to a transient state of underdigitalization.

Discussion

The use of rapidly injected NaEDTA appears to have greater value therapeutically than diagnostically. In 5 patients with digitalis-induced ventricular tachycardia, injection of NaEDTA was associated with reversion of the arrhythmia. In these patients relatively small doses of NaEDTA (0.5 Gm. or less) were effective. One patient with ventricular tachycardia, who had not received digitalis, did not revert after the administration of 1.2 Gm. of NaEDTA.

Ventricular arrhythmias unassociated with digitalis intoxication, however, may respond to NaEDTA (Case M.Z., trial 1). Gubner and Kallman12 and Kabakow and Brothers13 have also reported such instances. The latter investigators associated response with the presence of negative potassium balance. In the case reported herein, however, plasma potassium was normal and there was no suggestion of recent potassium loss.

Supraventricular arrhythmias failed to respond to NaEDTA in our study as well as that of Kabakow and Brothers. The arrhythmias were observed in all relationships to previous digitalis administration and plasma potassium levels. These results differ from those of Kabakow and Brothers, who thought that NaEDTA was effective in undigitalized patients with lowered potassium levels. It is noteworthy that the patient in whom they demonstrated this relationship had ventricular bigeminy and not a supraventricular arrhythmia. Gubner and Kallman reported 2 patients with atrial tachycardia with block who responded to infusion of NaEDTA. Potassium levels were not reported. Although the authors concluded that both these arrhythmias were supraventricular in origin, the abnormal configuration of the QRS complexes raises the possibility that they were ventricular. These results suggest that NaEDTA is unreliable, if effective at all, in the treatment of supraventricular arrhythmias no matter what the relationship to digitalis or potassium balance.

In general, we found a poor relationship between the dose of NaEDTA administered, the decrease in serum calcium produced, and the clinical response. NaEDTA was discontinued, however, when an effect was produced so that the patients who did not respond received larger doses of the drug. The occurrence of false positive and false negative results in ventricular arrhythmias, the lack of response in supraventricular arrhythmias, and the poor relationship between dose of NaEDTA and clinical or chemical response indicate that the response to NaEDTA injection is a poor guide to the degree of digitalization.

This defect does not preclude its usefulness in the therapy of ventricular arrhythmias. The use of procaaine amide, quinidine, or potassium therapy may be dangerous in patients with irritative ventricular arrhythmias. NaEDTA can be administered with little danger
Fig. 6 Top. Electrocardiograms in patient M. Z. showing ventricular bigeminy and response to NaEDTA.

Fig. 7 Bottom. Serial electrocardiograms in patient J. D. showing ventricular tachycardia (9:00 p.m.). Digitalis had never been administered. NaEDTA produced no change in the arrhythmia (9:04 p.m.). Following 0.8 Gm. of procaine amide intravenously, the rhythm changed to normal sinus (9:30 p.m.). Signs of congestive heart failure, present initially, persisted following restoration of normal sinus rhythm and the patient was successfully treated during the next 24 hours with a 500-ml. phlebotomy and 1.4 mg. of digitoxin. He was discharged 4 days later on 0.1 and 0.2 mg. of digitoxin on alternate days and 1.5 Gm. of procaine amide daily.
and may be the drug of choice in those ventricular arrhythmias clearly due to digitalis intoxication in the absence of potassium loss. Even in the presence of hypopotassemia NaEDTA may be a useful emergency measure prior to potassium replacement. The possibility exists that in patients with congestive heart failure, NaEDTA may reverse the beneficial effects of digitalis and precipitate pulmonary edema (patient M.Z.). Smaller doses of NaEDTA should be used in such instances.

SUMMARY

In 14 cases of cardiac arrhythmia, the chelating agent, disodium ethylene diamine acetate (NaEDTA), was administered in an attempt to bind serum calcium rapidly and, thus, to restore the previous cardiac mechanism. In 5 cases of ventricular tachycardia resulting from overtreatment with digitalis, the use of NaEDTA proved successful therapeutically.

The response to NaEDTA injection is a poor guide to the degree of digitalization. False positive and false negative results have been observed in ventricular arrhythmias. Supraventricular arrhythmias did not respond to NaEDTA, irrespective of the status of digitalis therapy and potassium balance. Clinical and chemical response was unrelated to the dose of NaEDTA.

For these reasons, it is concluded that intravenous NaEDTA while unreliable as a test agent, is valuable in the treatment of digitalis-induced ventricular arrhythmias.

ACKNOWLEDGMENT

We are indebted to Mrs. Ruth Aronson and Miss Carolyn Register for their technical assistance. Mr. Julius Lugovoy, Senior Chemist at Bellevue Hospital, kindly performed the determinations of serum calcium.

SUMMARIO IN INTERLINGUA

In 14 casos de arrhythmia cardiac, le agente chelatori dinatrium-ethylene-diamino-acetato (NaEDTA) eseva administrate con le objectivo de effectuar un ligation rapida de calcium sereal e de restaurar assi le previe mechanismo cardiac. In 5 casos de tachycardia ventriculare causate per excessos del dosage de digitalis, le uso de NaEDTA se provava un successo therapeutic.

Le responsa al injection de NaEDTA non es un satisfacente criterio pro le grado de digitalisation presente. Resultatos false positive e false negative ha esseite observate in arrhythmias ventricular. Arrhythmias supraventricular non respondeva a NaEDTA, sin reguardo al stato del digitalisation e del balancio de kalium. Le responsas clinie e chimie eseva sin relation al dosage de NaEDTA.

Pro iste rationes, le conclusion es formulate que administrationes intrvenose de NaEDTA es non digne de confidentia como test sed previo in le tractamento de arrhythmias ventricular inducte per digitalis.

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The occlusion of a catheterized ureter for a brief period of time and the collection of urine via a polyethylene tube after the occlusion is released permits a comparison of proximal and distal tubular function. This type of experiment was carried out in dogs before and after the administration of mercurial diuretics. An osmotic diuresis was maintained by a constant infusion of mannitol. Intravenous administration of thiomerin or meralluride caused at least a 50 per cent reduction in the mass of water and sodium reabsorbed by the proximal tubule during the brief period of occlusion. Reductions in water and sodium were equivalent, and the proximal tubule reabsorbate therefore had a sodium concentration similar to that of plasma. The mercurials did not alter the ability of the distal tubule to lower urinary sodium concentration during the period of ureteral occlusion. These studies suggest that the major effect of mercurial diuretics is on the proximal tubule and that their action may be to interfere with the passive reabsorption of sodium and water in this area of the nephron.

KAYDEN
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