Interrelationships Between Cardiac Effects of Ouabain, Hypocalcemia and Hyperkalemia

By Ernest Page, M.D. and Jack D. Real, A.B.

In dogs anesthetized with pentobarbital, ventricular arrhythmias induced by ouabain were consistently reverted to sinus rhythm by acute lowering of the serum calcium. In ouabain-intoxicated dogs, the depressed and shortened S-T segment was elevated and lengthened by induced hypocalcemia. Potassium administered concomitantly with ouabain exerted a protective effect against ouabain intoxication. Lowering of the serum calcium in animals showing moderately advanced potassium effects in their ECG precipitated acute, fatal potassium poisoning. Ouabain was capable of reversing the tachycardia and pulsus alternans due to hypocalcemia in the face of persistent hypocalcemic tetany.

Recent clinical and physiologic studies have re-emphasized the importance of the potassium ion in antagonizing the cardiac actions of digitalis. The apparent parallelism of the "physiologic antagonism" between the potassium and calcium ions with the antagonism between potassium ion and digitalis glycosides prompted a study of the effects of acute lowering of the serum calcium level on the electrocardiographic manifestations of ouabain intoxication in normokalemic and hyperkalemic dogs. Observations on the responses in the blood pressure and electrocardiogram of anesthetized dogs first rendered acutely hypocalcemic and then given either calcium or ouabain will also be presented. Acute hypocalcemia was produced by means of the di-sodium salt of ethylenediamine tetracetic acid (EDTA), a chelating agent, the in vivo calcium-binding properties of which have been well-described.

Procedure

The experimental subjects were 33 mongrel dogs, injected intraperitoneally with 120 mg. morphine sulphate two hours prior to the experiment, anesthetized with sodium pentobarbital 20-25 mg. per Kg. intravenously, and ventilated artificially at a rate of 20 per minute through an endotracheal tube. Electrocardiograms were observed throughout the procedure on a Sanborn Viso-Scope and recorded either on a direct-writing four-channel Sanborn "Poly-Viso Recorder" or on the Sanborn Twin-Beam Oscillograph. In some experiments blood pressure tracings were obtained with a heparinized catheter threaded via the carotid artery into the ascending aorta and recorded through a Sanborn Electro-manometer. Intravenous infusions were administered through a catheter in the external jugular vein.

Thirteen animals were given an infusion of ouabain, 0.5 mg. per 10 cc. in 5 per cent glucose, at a rate of from 4 to 6 cc. per minute, until oscilloscopic observation showed a persistent ventricular arrhythmia (repetitive ventricular premature beats, ventricular tachycardia, occasionally tachycardia with shortened P-R interval and prolonged intraventricular conduction time). Six animals, on which blood chemical determinations were later done, were given the same dosage of ouabain at the same rate diluted in only 40 cc. of 5 per cent glucose in order to minimize analytic inaccuracies due to hemodilution. After onset of the arrhythmia ouabain was stopped and EDTA (20 mg. per cc.) was infused at 8 to 10 cc. per minute until the arrhythmia was converted to sinus rhythm (see below), the EDTA being restarted at intervals as necessary to suppress recurrent ouabain-induced disturbances of rhythm. Blood samples for determination of serum calcium, magnesium, sodium and potassium were drawn from the surgically exposed right femoral vein before the procedure, after onset of the ouabain-induced arrhythmia, and one minute after reversion of the arrhythmia and discontinuation of EDTA. Disturbances of rhythm were produced in five additional animals with infusions containing ouabain 0.75 to 1.0 mg. per 100 cc. and potassium chloride in concentrations ranging from 5 to 10 mEq. per 100 cc.; the increased ouabain dosage was necessitated by the difficulty...
OUABAIN IN HYPOCALCEMIA AND HYPERKALEMIA

**Fig. 1.** Left, idioventricular rhythm induced by acute administration of ouabain in a hypocalcemic dog. Right, after rapid infusion of EDTA; Note reversion to sinus rhythm, alternation in appearance of the S-T segment and T-wave. Only every other QRS complex is followed by an arterial pulse wave (lower tracing).

| Table 1.—Serum Electrolyte Concentrations in mEq per liter |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Dog  | Blood Sample | Calcium mEq/L. | Magnesium mEq/L. | Sodium mEq/L. | Potassium mEq/L. |
| n24  | 1*           | 4.25           | 2.50            | 153            | 3.9             |
|      | 2t           | 5.83           | 0.35            | 153            | 4.0             |
|      | 3t           | 2.07           | 0.95            | 153            | 4.4             |
| n25  | 1            | 5.51           | 1.75            | 149            | 3.5             |
|      | 2            | 5.35           | 2.15            | 151            | 4.0             |
|      | 3            | 3.37           | 2.70            | 155            | 3.7             |
| n26  | 1            | 5.15           | 2.00            | 155            | 3.5             |
|      | 2            | 5.00           | 2.15            | 153            | 4.0             |
|      | 3            | 3.50           | 2.80            | 153            | 3.9             |
| n27  | 1            | 4.35           | 2.05            | 155            | 4.7             |
|      | 2            | 4.25           | 2.15            | 155            | 4.7             |
|      | 3            | 2.55           | 2.15            | 155            | 4.7             |
| n28  | 1            | 4.15           | 2.15            | 155            | 4.0             |
|      | 2            | 4.60           | 1.70            | 153            | 4.2             |
|      | 3            | 2.85           | 1.75            | 155            | 4.0             |
| n29  | 1            | 3.46           | 2.55            | 155            | 4.5             |
|      | 2            | 4.34           | 1.50            | 155            | 5.0             |
|      | 3            | 1.88           | 1.60            | 155            | 5.1             |

* Sample 1, control.
† Sample 2, after onset of ouabain-induced arrhythmia.
‡ Sample 3, one minute after reversion to sinus rhythm with EDTA.

In inducing ventricular arrhythmias due to ouabain in the presence of potassium ion.

In nine animals the order of the experiment was reversed; EDTA was first infused at 100 mg. per minute until the advent of three or more of the following: tachycardia, significant blood pressure changes, tetany, and S-T segment prolongation; these changes were then reversed by intravenous injection of calcium gluconate (0.5 Gm. in 5 cc). EDTA was thereupon infused to the previously noted end-point; in place of calcium gluconate, 0.5 mg. ouabain was now rapidly injected, and its effects on the hypocalcemic dog compared with those of calcium. In three of these dogs, blood for serum electrolytes as listed above was drawn before and after each EDTA infusion and following ouabain injection, allowing at least two minutes for equilibration after each infusion.

Serum calcium was determined by the method of Sobel and Hanok,† serum magnesium by the method of Orange and Rhein‡ and serum sodium and potassium by means of the Beckman Model DU spectrophotometer.

**RESULTS**

In every instance administration of EDTA at the rate described abolished the arrhythmia within two minutes and resulted in restoration of normal sinus rhythm with dramatic suddenness. Upon discontinuing the EDTA, the arrhythmia recurred, usually within three minutes, and could be abolished once more with EDTA. This cycle could be repeated as often as six times in a single experiment before disturbances of intraventricular conduction due to EDTA itself became apparent. After several repetitions of this procedure, the arterial pressure fell. Although normal sinus rhythm was restored with EDTA, pulsus alternans, often correlated with alternation in the appearance of the S-T segment and T-wave, was precipitated (fig. 1). Abolition of ouabain-induced
tachycardias was attended by relative elevation and prolongation of the S-T segment; after stopping EDTA, recurrent ventricular arrhythmias, i.e., recurrent ouabain toxicity, could be predicted by marked depression and shortening of the S-T segment and alternation in amplitude of the QRS complex (fig. 2 A and B). Abolition of the arrhythmias induced by ouabain was consistently attended by a pronounced fall in serum calcium, without clear-cut directional changes in serum potassium, sodium and magnesium (table 1).

Addition of potassium chloride to the ouabain infusion resulted in protection against ouabain poisoning, often necessitating doubling the dose of ouabain (to 2.0 to 2.5 mg.) before producing ventricular arrhythmias attributable to the glycoside. Administration of EDTA at the usual rate to animals manifesting signs of moderate potassium intoxication in their ECG (elevation and "tenting" of the T-wave, diminished P-wave amplitude or auricular standstill, early QRS prolongation) resulted in abrupt emergence of the ECG of terminal potassium poisoning with death of the animal.

Lowering the serum calcium level acutely with EDTA in dogs not pretreated with ouabain consistently induced a tachycardia of 130 to 160 beats per minute, a fall in pulse pressure and slowing of the carotid upstroke on the pulse tracing, development of pulsus alternans, and eventually tetany. The ECG showed variable T-wave changes and consistent prolongation of the S-T segment and T-wave and alternation in amplitude of the S-T segment (and hence, of the Q-T interval) relative to the increased heart rate, the S-T segment depression and shortening normally seen during tachycardia being apparently prevented by the hypocalcemic state. These qualitatively clear-cut changes, which were immediately reversible by calcium gluconate administration, do not lend themselves to quantitative measurement because of the well-known difficulty in exact delineation of the S-T segment and Q-T interval. It was found in 6 of the 9 dogs so studied that ouabain was capable of restoring the pressure to control or higher levels and of abolishing the pulsus alternans and tachycardia in spite of persistent hypocalcemia and in the face of frank tetany. S-T segment and T-wave changes after ouabaine were variable and returned to their control pattern (during hypocalcemia) in only two instances. Correlated chemical analysis in three dogs revealed a decrease in serum calcium levels after EDTA comparable in magnitude to the decreases recorded in table 1, the serum calcium returning to normal levels after calcium gluconate (but not after ouabain) administration.

**DISCUSSION**

It has been shown in such dissimilar tissue as skeletal muscle, nerve, erythrocytes and heart muscle that the digitalis glycosides and the calcium ion both act at the level of the cell membrane to alter cellular permeability to sodium and potassium. Calcium exerts major effects on the electrical stability of the polarized cell membrane, on which the magnitude, rate and direction of the potassium and sodium exchanges involved in depolarization and repolariza-
OUABAIN IN-HYPOCALCEMIA AND HYPERKALEMIA

zation of excitable tissues are in large part dependent. The abrupt precipitation in the present study of fatal potassium intoxication by acute lowering of the serum calcium in animals showing hyperkalemic effects in their ECG prior to EDTA administration would seem to indicate increased cellular permeability to potassium as a primary consequence of acute hypocalcemia. An alternative is to consider the classical electrocardiographic changes of hyperkalemia as not dependent on the extracellular potassium level alone, but as reflecting also the existing calcium-potassium ratio.

The prolongation and elevation of the S-T segment as a result of hypocalcemia and the shortening and depression of this deflection under the influence of ouabaine are of extraordinary physiologic interest. In basic electrophysiologic studies, the S-T segment of the surface cardiogram has been temporally correlated with the plateau of the cardiac action potential recorded from single heart muscle fibers by intracellular micro-electrodes and has been suggested as resulting from a temporary equalization of sodium and potassium permeabilities, the maintenance of which may require active expenditure of energy. This segment of the action potential, which appears to be remarkably sensitive to hypoxia, temperature and changes in heart rate, the control of which may be unrelated to cholinesterase inhibition, is altered characteristically in calcium deficiency and shortened by cardiac glycosides; the abnormalities induced by hypocalcemia are restored to normal by strophanthidin. The present experiments confirm for the whole heart in vivo, that, in the presence of ouabaine toxicity, the S-T segment is affected oppositely by hypocalcemia and ouabain. Moreover, it was evident that extreme changes in the S-T segment in the case of both ouabain (depression and shortening) and hypocalcemia (prolongation and elevation, encroachment on the T-wave) proceeded in an apparently predictable manner disturbances of ventricular depolarization (QRS) and the appearance of ventricular arrhythmias. A portion of our findings relating to abolition of digitalis arrhythmias with EDTA is in agreement with results published in a recent abstract by Smith and Grinnell.

In 1917, Loewi interpreted the action of digitalis on the amphibian heart as one of "sensitization" of the heart to calcium. Since then numerous clinical and experimental reports have debated the question of calcium-digitalis "synergism." The similar effects of cardiac glycosides and calcium in inducing cardiac slowing and ventricular fibrillation, as well as the ability of both agents to protect against potassium poisoning have been delineated. In this connection, the present study does not support an unqualified parallelism between the effects of ouabain and calcium at hypocalcemic levels. Ouabain, unlike calcium, did not consistently return both the electrocardiogram and arterial pulse tracing to control levels, nor was its action during hypocalcemia as rapid as that of calcium.

SUMMARY

In dogs anesthetized with pentobarbital, ventricular arrhythmias induced by ouabain were consistently reverted to sinus rhythm by acute lowering of the serum calcium with disodium ethylenediamine tetra-acetic acid.

In ouabain-intoxicated dogs, the depressed and shortened S-T segment was elevated and lengthened by induced hypocalcemia.

Potassium administered concomitantly with ouabaine exerted a protective effect against ouabaine intoxication. Lowering of the serum calcium in animals showing moderately advanced potassium effects in their ECG precipitated acute, fatal potassium poisoning.

Ouabain was capable of reversing the tachycardia and pulse alternans due to hypocalcemia in the face of persistent hypocalcemic tetany.

REFERENCES


3 Popovic, A. Geschickter, C. F., Rebovicsky, A. and Rubin, M.: Experimental control of


Interrelationships Between Cardiac Effects of Ouabain, Hypocalcemia and Hyperkalemia

ERNEST PAGE and JACK D. REAL

doi: 10.1161/01.RES.3.5.501

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1955 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/3/5/501

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/