A Study of the Digitalis-like Action of Thevetoidin in Man

By Ignacio Chavez, M.D., Rafael Méndez, M.D., and Leonardo O. Chait, M.D.

The effect of thevetoidin in heart failure has been studied. Thevetoidin has a prompt and partly transient digitalis-like effect which is shown on the heart rate, the circulatory velocity and on the P-R and Q-T intervals of the electrocardiogram, and also a cumulative effect similar to that of strophanthin. Due to its intense vagal effect and its quick digitalis-like action, paroxysmal auricular tachycardia was stopped in two patients out of three in from three to four minutes. Its therapeutic advantages and disadvantages are discussed.

A NEW cardioactive substance, thevetoidin, has been isolated from Thevetia gaumeri, in the Department of Physiology and Pharmacology of the National Institute of Cardiology, Mexico. Thevetia gaumeri, which grows in various states of the Mexican republic, was identified botanically by Martínez in Mexico and by Woodson in the United States. The chemical extraction of thevetoidin from the seeds of this plant was accomplished by E. Sodi-Pallares and R. Mendez and the pharmacologic study was done by Mendez and collaborators.

Thevetoidin is a white, crystalline, moderately hygroscopic powder. Recent chemical studies still in progress have shown that the thevetoidin used in the present work contains a cardiac glycoside, acetylstrophanthin, and a small amount of a quaternary ammonium base which has been identified as diaetylithosomuscine. Pharmacologic studies revealed that this substance in a concentration of $1 \times 10^{-4}$ caused systolic arrest of the frog heart (method of Straub-Fuehrer) in 20 minutes. The arrest was shown to be reversible on washing with Ringer’s fluid. The minimum lethal dose in the frog obtained by the official method of the U.S.P. XIII is 2.6 mg. and by the method of Hatcher and Brody (technic of Storm van Leeuwen), 2.3 mg.

Experiments carried out by one of us (R. M.) in the insufficient heart of the heart-lung preparation, 8 have shown that thevetoidin can reverse experimental cardiac insufficiency, whether spontaneous or induced by pentobarbital. In a dose of 0.8 mg. the effect was transient, failure reappearing within 50 to 60 minutes in the same degree as existed before administration of the drug. In the dog anesthetized with pentobarbital (20 mg. per Kg.) and chloralose (80 mg. per Kg.) a dose of thevetoidin of 0.5 to 0.6 mg. per Kg. produced toxic effects which consisted of bradycardia and prolongation of the P-R interval, followed by auriculoventricular dissociation and multifocal ventricular extrasystoles. These toxic effects on ventricular automatism disappeared rapidly and the P-R interval returned to its normal duration within approximately one to two hours.

With these data as a background we undertook a clinical study of thevetoidin, believing that we were dealing with a substance with a very rapid transient action similar to that of thevetin and of acetylstrophanthin studied by Gold and collaborators. 9, 10 However, analysis of the cases which we present in this paper demonstrates that the new substance possesses, in addition to the rapid and transient action revealed in the pharmacologic study, a cumulative tendency similar in degree to that of strophanthin. 11

Case Material

The clinical results which constitute the theme of this preliminary work have been obtained in 10 patients with rheumatic heart dis-
ease, seven of whom were in a state of cardiac insufficiency and three of whom had paroxysmal auricular tachycardia. Of those patients in heart failure, two had mitral and tricuspid valvular disease with auricular fibrillation but without active rheumatic disease; two had similar lesions with fibrillation and active rheumatic disease; one patient with lesions of the mitral, aortic, and tricuspid valves had a normal sinus rhythm and an active rheumatic process; one had mitral stenosis and regurgitation and one had lesions of the mitral and aortic valves, both having sinus rhythm and inactive rheumatic disease.

METHODS

The patients (except those treated for paroxysmal auricular tachycardia) were maintained at rest for several days before experimentation. In only one patient had any preparation of digitalis been administered for at least 10 days previously. The heart rate and electrocardiographic changes were carefully recorded. In the patients with fibrillation, measurements of the Q-T interval were studied in groups of 10 beats, relating each Q-T interval with the preceding R-R interval. The circulation time was measured by means of potassium cyanide. Thevetoidin was always administered by vein. Due to the hygroscopic nature of the substance the thevetoidin was stored in evacuated ampoules and dissolved in a volume of 1 or 2 cc. of physiologic saline immediately before injection.

RESULTS

Group 1

(a) Patients with Mitral and Tricuspid Lesions and Auricular Fibrillation, but without Active Rheumatic Disease (two cases). The first patient (No. 18610.B2), a girl 18 years of age weighing 48.2 Kg., had been hospitalized several times in the Institute of Cardiology and on each occasion was treated by the classic methods of digitalization. The second (No. 23673.B3), a woman 25 years of age weighing 50 Kg., hospitalized for the first time, was treated first with thevetoidin and several days later with Digilanid. Due to the advanced state of the lesions of these two patients, the improvement which was obtained in the clinical signs with Digilanid and with thevetoidin, although clear, did not constitute a dramatic reversal of the cardiac insufficiency. However, slowing of the heart rate, decrease in liver size, and reduction of jugular engorgement, of edema, and of effort dyspnea with resulting subjective improvement, were as great with thevetoidin as with Digilanid.

Figure 1 shows the changes of heart rate in one of these women after daily injections of thevetoidin. Each injection of 10 mg. (0.2 per Kg.) caused a decrease in the heart rate. The dots on the graph show control rates taken just before each injection. In figure 1 the rate is seen to decline from 130 to 73 after the ad-

![Figure 1. Cumulative action on the heart rate of repeated injections of thevetoidin. REG. 18610, 18 year, 48.2 Kg. Inactive rheumatic valvular disease, mitral stenosis and regurgitation, tricuspid insufficiency, auricular fibrillation, and cardiac insufficiency grade III.](image-url)
response was obtained within 10 to 12 minutes after each injection. The effect on the heart rate regressed slowly after this time but the heart rate on the day following the injection was always less than that before injection until, after repeated doses, it was reduced to a controlled level. That is to say, thevetoidin appears to exert a double effect: the first rapid, with a maximum effect at 10 to 12 minutes after injection, and the second slow and cumulative. Figure 1 demonstrates this latter action and figure 2 illustrates the former. The irregularity in the heart rate shown in figure 2 was due to a brief period of vomiting which occurred four minutes following the administration of thevetoidin.

An early effect was observed on the Q-T interval of the electrocardiogram, an effect which disappeared almost completely one to two hours after the first dose of thevetoidin. Subsequent injections showed a cumulative effect to which we have already referred in describing changes of heart rate. After the second or third dose, there appeared in these patients depression of the S-T segment similar to that observed with the cardiac glycosides; these effects did not regress until three or four days following termination of the treatment.

(b) Patients with Auricular Fibrillation, Mitral and Tricuspid Lesions, and Active Rheumatic Fever (two cases). One (No. 1 REG. 10935.C39) was a youth of 15 years weighing 33.2 Kg.; and one (No. 2 REG. 10988.B13), a 43 year old mother weighing 47.4 Kg.

The same, or even one-half, of the amount of the drug administered to the two previous patients frequently caused extrasystoles and at times bigeminal rhythm lasting for 10 to 50 minutes in these two patients with active rheumatic fever. Injection was occasionally followed by mild subjective discomfort such as vague discomfort in the precordial region, sensations of heat, pain in the eyes, or paresthesias in the extremities. These sensations disappeared quickly. In the last days of treatment there was observed a more prolonged bigeminal rhythm, with persistence of extrasystoles until the day following the injection.

The manifestations of toxicity in these two patients with active rheumatic disease are to be contrasted with the results obtained in the two patients without rheumatic activity, in whom no effect whatsoever on ventricular rhythm was observed during the 10 days of treatment with daily doses of 0.2 mg. per Kg.

(c) Patients without Rheumatic Activity and with Sinus Rhythm (two cases). The first (REG. 22241.C8), a girl of 15 years weighing 34.2 Kg., with mitral stenosis and regurgitation, received single doses of 5 mg. of thevetoidin daily for four days. Before beginning treatment the heart rate was 102 beats per minute; a presystolic gallop was present. The liver was palpated 3 cm. below the costal border in the midclavicular line and presented grade II pulsations. The circulation time measured with potassium cyanide was 26 seconds (normal, 18 seconds). Roentgenograms of the chest showed grade III cardiac enlargement and pulmonary congestion. On the second day of treatment the heart rate had been reduced to 80 beats per minute with disappearance of the gallop rhythm. The liver regressed to no more than 1 cm. below the costal border and pulsations were estimated at no more than grade I. The circulation time was
reduced to 19 seconds. On the third day the liver had regressed to the costal margin and was no longer felt to pulsate. On the fourth day the circulation time was 16 seconds and x-ray examination demonstrated a definite diminution of the cardiac shadow and of pulmonary congestion (fig. 3).

On the last day when the patient had received a total of 20 mg. of thevetoidin there were occasional extrasystoles and nausea, about three minutes after the injection, which rapidly disappeared. Hours later, vomiting occurred.

On the P-R interval and the Q-T interval in this case are presented graphically in figure 4.

The second case (REG. 18676.C36), a boy of 15 years, weighing 34.5 Kg., with mitral stenosis and regurgitation and aortic insufficiency, received single daily doses of 5 mg. of thevetoidin during a period of three days. Due to the development of vomiting the dose was reduced to 3.5 mg. daily during the six following days. This dose produced no emetic action. Before treatment the heart rate was 104 beats per minute with a presystolic gallop. The liver

In this patient digitalis-like effects on the Q-T interval similar to those in preceding cases were also observed; to this effect was added prolongation of the P-R interval which increased from 0.18 second as measured on the first day to 0.21 second on the fourth day. The P-R interval returned to the original value of 0.18 second four days after termination of treatment. The early brief action of the drug could be demonstrated also with respect to this measurement, for on the third day it increased from 0.20 second to 0.23 second seven minutes following the injection, only to return to 0.21 second 30 minutes later. The cumulative effects margin was palpated 10.5 cm. below the costal border in the midline and 6 cm. in the midclavicular line with grade II pulsations. The venous pressure was 23 cm. of water. The circulation time measured with potassium cyanide was 26 seconds. Twenty-eight minutes following the first injection the circulation time was reduced to 20 seconds.

On the second day the liver margin was 9.5 cm. below the costal margin in the midline and 5 cm. in the midclavicular line; pulsations were reduced to grade I. Except for delayed vomiting no other changes were reported. On the third day the heart rate was 98 per minute and

Fig. 3 Reduction of area of cardiac silhouette after daily injections of 5 mg. during four days. The silhouette after injection has been drawn on the figure on the right. REG. 22241, 15 years, 34.2 Kg. Inactive rheumatic valvular disease; mitral stenosis and regurgitation; sinus rhythm. Cardiac insufficiency grade II.
vomiting occurred one minute following the injection preceded by an ill defined taste and a sensation of numbness in the lower lip. Vomiting occurred again later. On the fourth day the dose was reduced to 3.5 mg. Nausea and a mild pain in the eyeballs appeared after the injection but rapidly receded. The circulation time was reduced to 19 seconds. On the fifth day the liver edge was palpated at 8.5 cm. below the costal margin in the midline and only 2.5 cm. in the midclavicular line; pulsations were no longer observed. The heart rate was 92 per minute but the gallop rhythm persisted. From the sixth to the ninth day no further variations were observed. On this last day two doses of 3.5 mg. each were administered. A second bout of repeated vomiting lasting several hours followed.

On the tenth day, when treatment was terminated, the heart rate was 90 per minute. Gallop rhythm persisted and the liver was palpated 7.5 cm. below the costal border in the midline and 2 cm. in the midclavicular line. Pulsations were not detected. Circulation time was 20 seconds. Venous pressure was 18 cm. of water. No significant changes were observed in the cardiac size.

The most marked changes in this case were the reduction of liver size and pulsation and of the circulation time and the venous pressure. It is to be emphasized that the diminution of six seconds in the circulation time obtained following the first dose was not improved with subsequent doses. The effects on the P-R and Q-T intervals were similar to those found in the other patients.

**Group 2**

*Paroxysmal Auricular Tachycardia* (three cases). The rapid action of thevetoidin with its strong vagal component observed experimentally and in some patients suggested to us the possibility of its use in paroxysms of auricular tachycardia. The first patient, C8, a 15 year old girl weighing 30 Kg., with inactive rheumatic fever and grade I cardiac insufficiency, received an injection of 6 mg. which restored sinus rhythm in four minutes. Paroxysmal tachycardia did not recur during our observation. In the second case, B2, a 16 year old girl weighing 40 Kg., with active rheumatic disease, a dose of 8 mg. caused no effect whatsoever. Six hours later she received 10.5 mg. Two and one-half minutes following this dose there appeared 2:1 and 3:1 A-V block which lasted three minutes; later 1:1 rhythm was reestablished with a prolonged P-R interval, but the paroxysm of tachycardia was not terminated. The third case, C. E., a youth of 20 years weighing 60 Kg. with active rheumatic disease, received 12 mg. Tachycardia ceased within three minutes.

**Dosage and Secondary Effects**

A daily dose of 0.2 mg. per Kg. of body weight produced complete digitalis-like effects in three or four days. A single injection of 10 mg. in patients weighing approximately 50 Kg. produced nausea and vomiting in almost every case. The time of appearance of this side effect varied between 2 and 15 minutes and the episode was in general of no more than a few minutes duration. Division of the dose into two injections per day each of 0.1 mg. per Kg. with an interval of several hours
between the two injections, almost always prevented the appearance of vomiting. In only one case was a moderate and brief period of nausea observed under this method of administering the drug. In general, children tolerated the strong dose of 0.2 mg. per Kg. better than adults and only on rare occasions was vomiting observed. Other mild transient secondary side effects, such as paresthesias, ocular pain, and a sensation of heat, were observed only occasionally.

We have made no systematic attempt to obtain a rapid digitalis-like effect in less than three days. We believe, however, that with doses appropriately divided full effects of the drug may be obtained in 24 hours or less. In one adult patient with auricular fibrillation, who received 17.5 mg. divided in two injections given six hours apart, a reduction of heart rate from 130 to 80 was achieved.

Demonstration of the Transient Nature of the Toxic Action

One male patient, weighing 36 Kg., with paroxysmal auricular tachycardia probably due to digitalis intoxication, received by error 9 mg. of thevetoidin. One minute later there appeared a salvo of ventricular extrasystoles from four foci. Four minutes after the injection the extrasystoles were less frequent, originating from only two foci, and there was 3:1 and 2:1 A-V block. Five minutes after the injection extrasystoles had disappeared but a 2:1 A-V block persisted. Eight minutes after injection an episode of auricular fibrillation of only one minute duration appeared. By 10 minutes much of the evidence of intoxication had disappeared. The auricular tachycardia continued.

Discussion

The results demonstrate that thevetoidin possesses a typical digitalis-like action and that within this general action there may be distinguished two different effects. The first is characterized by an early, rapid and partially reversible action on the heart rate, A-V conduction, the Q-T interval and by the production of brief toxic effects (transient extrasystoles, nausea and vomiting). The second effect is characterized by a cumulative action similar to that of strophanthin.

Pharmacologic study of thevetoidin demonstrated the first of these two actions. With appropriate doses the action on the insufficient heart in the heart-lung preparation was very rapid: the effect reached a maximum in approximately 10 minutes only to diminish progressively until within an hour insufficiency of the degree present before injection was reestablished. This rapid action and its early disappearance were confirmed by experiments on anesthetized dogs in which digitalis-like toxic effects produced by one injection of thevetoidin rapidly disappeared. The later and more persistent effect has been demonstrated by the clinical studies described in the present paper. These studies showed that in addition to the rapid action a clear cumulative effect develops which suggests one of the two following possibilities: first, that thevetoidin possesses two different effects, one brief and one persistent; second, that thevetoidin contains two substances each responsible for one of the two effects. Since thevetoidin has recently been shown to contain small amounts of a muscarin derivative in addition to a cardiac glycoside, the early effect might be due to the combination of the action of the quaternary ammonium base with the fast-acting glycoside. The vagal effect caused by the quaternary ammonium base should at least be partly responsible for the effect in patients with paroxysmal auricular tachycardia.

The small number of cases studied does not permit us to fix precisely the limits of dosage. However, it appears almost certain that one may expect adequate digitalis-like effects with the administration of 0.2 mg. per Kg. divided in one, or better two, daily injections during three or four consecutive days.

While considering dosage it is important to discuss the side effects of the drug. The mild subjective symptoms described are brief and of only minor significance. On the other hand, the frequency of vomiting marks thevetoidin as a digitalis-like substance which provokes this side effect with great facility. Clinically, this constitutes a great inconvenience. Fortunately, we have found that dividing the dose or reducing it
slightly lessens or even eliminates vomiting. The results obtained with the prophylactic administration of Dramamine to two patients suggest the use of this drug to avoid vomiting following the administration of thevetoidin.

With respect to its surprising speed of action thevetoidin possesses a great advantage over strophanthin, being comparable only with thevetin and acetylstrophanthinid, as studied by Gold and collaborators. Thevetoidin, however, possesses a cumulative action. It is not apparent from the studies of Gold whether thevetin and acetylstrophanthinid are similar in this respect since their experiments were limited to observation of acute effects of a single injection on the heart rate without electrocardiographic records or observation of changes in the degree of cardiac insufficiency.

The speed of action of thevetoidin is unsurpassed by any other known cardiac drug. The drug slows the heart rate, increases the circulatory velocity and improves the work of the heart. It has not been used in the treatment of acute cardiac failure for fear of its emetic effect. A glycosidic substance purer than thevetoidin will shortly be used for the treatment of this condition.

By virtue of its cumulative action, which prolongs its effects for several days, thevetoidin has proved to be very efficacious in the treatment of chronic cardiac insufficiency. In the course of three or four days we have been able to achieve digitalis-like effects with variable results according to the type of the patient treated; in some elimination of cardiac insufficiency was complete, in others only improvement was obtained, but in the latter cases the complete correction of insufficiency was impeded by the presence of advanced tricuspid lesions or rheumatic activity. Furthermore, in these same patients digitalis itself failed to restore a complete state of compensation. The major advantage of thevetoidin in cases of chronic insufficiency appears to be based on the low incidence with which persistent arrhythmias are produced. Patients who were unable to tolerate digitalis because of the rapid development of bigeminal rhythm have responded well to thevetoidin with only occasional transient extrasystoles. One patient already intoxicated with digitalis who received by accident a dose of thevetoidin developed an arrhythmia, but this disappeared in the course of only a few minutes while arrhythmia due to digitalis may be expected to last for a long time.

It seems apparent that thevetoidin may be a product more controllable than digitalis in the early cardiac insufficiency following myocardial infarction. In this situation fear of provoking grave arrhythmias at times prevents the use of digitalis. Thevetoidin could be equally useful but less dangerous. Later studies will permit us to confirm or deny this point.

**Summary**

Thevetoidin, a cardioactive substance obtained from a Mexican species of *Thevetia* has been subjected to clinical study. This study has been carried out in 10 rheumatic patients, seven of whom were in a state of cardiac insufficiency with or without auricular fibrillation, and three of whom had paroxysmal auricular tachycardia.

The results obtained with thevetoidin in cardiac insufficiency were analogous to those obtained with digitalis in the same patients.

Of the three patients treated during paroxysmal tachycardia, normal sinus rhythm was restored in two within three to four minutes following injection of the drug.

Thevetoidin has an early action on heart rate, on circulatory velocity, and on the P-R and Q-T intervals of the electrocardiogram, effects which reach their maximum within 10 to 12 minutes. In addition to this early action it possesses a cumulative effect similar to that of strophanthin which permits the satisfactory treatment of chronic cardiac insufficiency. The transient nature of the effects of thevetoidin is apparent with respect to the early toxic manifestations, such as vomiting and ventricular extrasystoles.

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