An Evaluation of Digitalis Tolerance
with Acetyl Strophanthidin

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The determination of the state of digitalization in a given patient is often
difficult and at times impossible. Although Eggleston\(^1\) indicated that the
required quantity of digitalis is a function of body weight, the digitalizing
dose is an empiric and occasionally a dangerous assumption. Clinically,
the classical symptoms of digitalis intoxication may mimic those of cir-
culatory failure. Nausea, vomiting, and abdominal distress may be sec-
ondary to hepatic and visceral congestion; premature ventricular systoles
may be a manifestation of myocardial anoxia; and paroxysmal tachycardia
may indicate excessive or inadequate digitalis administration. The electro-
cardiogram indicates digitalis effect, but no quantitative correlation with
the S-T segment and T wave changes exists. Only with the electrocardio-
graphic appearance of auriculoventricular block, premature ventricular
systoles, bigeminus rhythm, nodal rhythm, etc., is toxicity apparent.

It, therefore, becomes evident that the need for a test designed to es-
blish proper digitalization exists. In an attempt to fulfill this need, Lown
and Levine\(^2\) recently described the acetyl strophanthidin test, employing
the synthetic ester of the cardiac aglycone, strophanthidin, obtained from
the seeds of Strophanthus kombe (Fig. 1).

That acetyl strophanthidin possesses a digitalis-like action has been ex-
tensively proved. Chen and Elderfield\(^3\) produced systolic standstill of the
frog ventricle and emesis in cats following sublethal doses administered
intravenously. Greiner and Reilly\(^4\) demonstrated myocardial contraction
as judged on an isolated hypodynamic papillary muscle. Gold et al\(^5\) found
that acetyl strophanthidin produced essentially the same kind of effects
as the digitalis glycosides in man, such as slowing of the ventricular rate
in atrial fibrillation, nausea, vomiting, and alleviation of the symptoms of
cardiac failure. That it potentiates ouabain in the production of ventricular
tachycardias has been well shown by Enselberg et al.\(^6\)

The attempt to determine the state of digitalization by the employment
of an additional intravenous glycoside is not new. In 1943, LaDue and
Fahr\(^7\) employed lanatoside C, but the delayed action of this drug militates
against its practical value. Griffith\(^8\) employs 0.5 mgm. of ouabain diluted
to 20 cc., injecting at the rate of 1 cc. per minute. When the cardiac rate
slows perceptively, he feels he is getting good digitalis effect; if an ar-
rhythmia or tachycardia ensues, toxic effects are presumed to have oc-
curred and the ouabain test dose is discontinued.

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The advantage of a preparation possessing a short latent period of action and rapid dissipation becomes evident by comparison of acetyl strophanthidin with ouabain (Table I). Acetyl strophanthidin exerts its earliest effect within $\frac{1}{2}$ to five minutes, reaches its peak action at 12 minutes, and is dissipated completely in two hours. The effect of ouabain is clinically first noted at five to 20 minutes, reaches its peak at one to two hours, and is completely eliminated from three hours to five days. The advantages of acetyl strophanthidin, therefore, are its short latent period, short dissipation, and short period of potential toxicity.

**Technique of Acetyl Strophanthidin Digitalis Tolerance Test**

Two cc. of acetyl strophanthidin (6 cat units or 1.1 mgm.) is diluted to 20 cc. with 5 per cent glucose in water. If the patient has received small amounts or no digitalis, 5 cc. is injected intravenously every five minutes until the desired therapeutic effect or toxic effect electrocardiographically appears. For those patients who have been digitalized, the dosage interval may be lengthened to 10 minutes, although in our cases a five-minute dosage interval proved satisfactory. These effects are followed by means of a continuous direct-writing electrocardiograph.

According to Lown and Levine's experience with 20 tolerance tests, if toxicity developed after the first injection of 0.27 mgm. of acetyl strophanthidin, over-dosage was present. If toxicity ensued after 0.55 mgm. the patient was considered to be adequately digitalized. When therapeutic action occurred after 0.82 mgm., fractional doses of digitalis were indicated, and if 1.1 mgm. or more was required, full digitalization was necessary. Evidence of acetyl strophanthidin over dosage consisted of the appearance of ventricular premature systoles, acceleration of the auricular rate, changes in the contour of the P wave, and prolonged auriculo-ven-
TABLE I
COMPARISON OF SPEED OF ACTION AND DISSIPATION OF OUABAIN AND ACETYL STROPHANTHIDIN*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Earliest Effect</th>
<th>Peak Action</th>
<th>Persistence of Effect</th>
<th>Duration of Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouabain</td>
<td>5 - 20 min.</td>
<td>60 - 120 min.</td>
<td>3 hr. - 5 days</td>
<td>Several hr.</td>
</tr>
<tr>
<td>Acetyl strophanthidin</td>
<td>½ - 5</td>
<td>12</td>
<td>2 hr.</td>
<td>30 min.</td>
</tr>
</tbody>
</table>

*Note that action of acetyl strophanthidin is more rapid and more transient than that of ouabain.


tricular conduction. In the presence of atrial fibrillation, the acceleration and regularization of the ventricular response indicating atrial tachycardia with block was considered significant.

Our plan was to evaluate the degree of digitalization and proximity to toxicity in patients receiving different preparations. Consequently, for this test a group of 10 patients presenting various etiologic forms of heart disease were selected. They were digitalized and maintained on either whole-leaf digitalis or digoxin. All had apparently been well digitalized as evidenced by slowing of the ventricular rate, objective and subjective subsidence of symptoms of congestive heart failure, along with the main-

FIGURE 2: Patient R. G. N., age 65, arteriosclerotic heart disease on digoxin 0.50 mgm. All leads are lead II. IIa—No change immediately after 0.82 mgm. acetyl strophanthidin. IIb and IIc—Note development 2 minutes later of premature ventricular systoles of multi-focal origin. IIId—Abolishment of premature ventricular systoles with 10 mgm. pronestyl intravenously.
tenance of a so-called “dry weight” for a minimum period of two weeks. In all instances, electrocardiographic evidence of digitalis effect upon the S-T segment and T wave was evident as compared to the initial pre-digitalization electrocardiogram.

Results of Test. Ten patients were tested by the aforegoing method: four patients with chronic cor pulmonale, four with arteriosclerotic heart disease, and two with hypertensive cardiovascular disease.

In this group of 10 apparently well-digitalized patients, electrocardiographic evidence of toxicity was achieved in only two. In one (Fig. 2) after 0.82 mgm. of acetyl strophanthidin, frequent multi-focal premature ventricular systoles were noted. This occurred in a 65-year-old white man with arteriosclerotic heart disease and indicated that he had incomplete digitalization and would require small further fractional doses of digitalis. The arrhythmia ceased after 100 mgm. of procaine-amide was administered intravenously.

In the second case (Fig. 3), a 41-year-old white man with chronic cor pulmonale, a transient nodal rhythm developed after 0.82 mgm. of acetyl strophanthidin. Again this test indicated incomplete digitalization.

In six cases, no change in the electrocardiographic pattern was noted with the administration of 1.1 mgm. of acetyl strophanthidin. In two cases, even 1.65 mgm. failed to produce electrocardiographic toxicity.

Conclusion

In our experience, the acetyl strophanthidin tolerance test possesses value in clinical cardiology only as an indicator as to whether or not more digitalis can be tolerated safely. This data may be of paramount significance in patients where digitalis has been taken erratically, where a supraventricular tachycardia or frequent premature systoles exist. That a significant and variable margin exists between the therapeutic and toxic doses is evident and has been emphasized previously. LaDue⁷ was able to administer 1.6 mgm. of lanatoside C to fully digitalized patients. In our experience, full digitalizing doses of acetyl strophanthidin in similar patients elicited toxicity in only two of 10 cases. Lown⁸ refers to this

FIGURE 3: Patient H. S., age 41, with chronic cor pulmonale on 0.5 mgm. digoxin (Lead IIa). Lead IIb—Note development of nodal rhythm after 0.82 mgm. acetyl strophanthidin.
safety margin as the “insensitive area in the dosage response curve of
drug action.” In this relatively small number of cases, there were no
apparent differences in the approach to toxicity with whole-leaf digitalis or
digoxin. Lown and Levine’s data which indicate that groups of patients
could be segregated on the basis of no digitalis, partial, complete, or ex-
cessive digitalization could not be confirmed. Moreover, it is unlikely in
view of the wide and variable range between minimal adequate digitaliza-
tion and toxicity in the individual patient that such a degree of accuracy
could be obtained with any preparation.

Acknowledgments: The authors wish to express their appreciation to Eli Lilly and
Company for their generous supply of acetyl strophanthidin.

SUMMARY

1. Experiences in ten digitalized patients utilizing acetyl strophanthidin
as a digitalis tolerance test are related.

2. In eight of the ten cases, toxicity could not be elicited with full digi-
talizing doses of acetyl strophanthidin in previously adequately digitalized
patients. This was true whether whole-leaf digitalis or digoxin was
employed.

3. The acetyl strophanthidin test will indicate whether additional digi-
talis may be safely administered. It does not indicate the state or adequacy
of prior digitalization. One cannot determine by this method, therefore,
whether the patient has received any digitalis or is partially or completely
digitalized.

RESUMEN

1. Se relatan las experiencias en diez enfermos digitalizados usando
acetil-estrofantidina como prueba de tolerancia a la digital.

2. En ocho de los diez casos no se pudo provocar la toxicidad con dosis
completas digitalizantes de acetil-estrofantidina en enfermos previamente
y adecuadamente digitalizados. Ocurrió esto tanto cuando se usó hoja
completa de digital como cuando se usó digoxina.

3. La prueba de la acetil-estrofantidina indicará cuando pue de pro-
porcionarse más digital con seguridad. No indica el estado de la digitali-
zación previa ni si está es adecuada. Por tanto, no se puede saber por este
método si el paciente ha recibido digital o esparcial o completamente digi-
talizado.

RESUME

1. Les auteurs rapportent une expérience d’utilisation de l’acetyl-stro-
phantidine comme test de tolérance chez 10 malades traités par la digi-
taline.

2. Dans huit de ces 10 cas, la toxicité ne put être mise en évidence avec
des doses d’acetyl-strophanthidine susceptibles de réaliser une digitalisa-
tion complète chez des malades antérieurement traités par la digitaline. 
Ceci fut vrai quelle que soit la préparation de digitaline utilisée.

3. Le test à la strophanthidine permet de savoir si une dose supplémen-
taire de digitaline peut être administrée sans risque ou non. Il n’indique
pas l’état de “digitalisation” antérieure. C’est pourquoi on ne peut déterminer par cette méthode si le malade a reçu antérieurement une certaine dose de digitaline, ou bien s’il subit partiellement ou de façon complète l’action de ce produit.

ZUSAMMENFASSUNG

1. Es werden Erfahrungen mitgeteilt an 10 digitalisierten Kranken unter Verwendung von Acetyl-Strophanthidin als Digitalis-Toleranz-Test.
2. Bei 8 der 10 Fälle konnte die Toxizität mit voll digitalisierenden Dosen von Acetyl-Strophanthidin bei zuvor entsprechend digitalisierten Kranken nicht festgestellt werden. Dies war der Fall, gleichgültig, ob Digitalis-Vollextrakte oder Digoxin benutzt wurde.
3. Der Acetyl-Strophanthidin-Test ergibt, ob noch zusätzlich Digitalis ohne Schädigung verordnet werden kann. Er zeigt aber nicht das Ausmass oder die Zulässigkeit vorheriger Digitalisierung an. Man kann daher mittels dieser Methode nicht feststellen, ob der Kranke überhaupt Digitalis erhalten hat oder teilweise oder vollständig digitalisiert ist.

REFERENCES

8. Griffith, G. C.: Personal communication from George C. Griffith, University of Southern California School of Medicine.
9. Lown, B.: Personal communication from Bernard Lown, Department of Medicine, Harvard Medical School.