CASE REPORTS

Digitalis and the Sick Sinus Syndrome
Clinical and Electrophysiologic Documentation of a Severe Toxic Effect on Sinus Node Function

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SUMMARY
Digoxin, in a common clinical dose and at a low serum level, brought out severe manifestations of sinus node dysfunction in a patient who had previously undergone successful mitral valve replacement. This report presents the results of extensive clinical and electrophysiologic studies of this patient before and after a digoxin challenge. In the absence of cardiogenic glycoside, the only demonstrable abnormalities of sinus node function were mild resting sinus bradycardia and failure to respond to atropine administration. Responses to isoproterenol administration, programmed premature atrial stimulation, and overdrive pacing at several cycle lengths were normal. Following the administration of intravenous digoxin, 1.025 mg/24 hrs, the resting sinus cycle length increased and the response to overdrive pacing became markedly abnormal. The latter was followed by sinus pauses in excess of six seconds, even at relatively slow overdrive pacing rates. The electrophysiologic and clinical implications of these data are discussed. It is suggested that despite previous reports that digitalis preparations are relatively well tolerated by patients with sick sinus syndrome, caution should be used when administering these drugs to this group of patients.

Additional Indexing Words:
Premature atrial stimulation
Rapid atrial pacing
Isoproterenol
Atropine
Sinus pauses
Sinoatrial block

The clinical manifestations of the syndrome of sinus node dysfunction have been described in detail in recent years. Since the report of Short et al. that emphasized the undue sensitivity of two of four patients with alternating periods of bradycardia and tachycardia to quinidine, we have begun to appreciate that all antiarrhythmic drugs are capable of inducing profound sinus bradycardia and even sinus arrest in some patients with sinus node dysfunction. The mechanisms underlying this undue sensitivity of the sinus node to antiarrhythmic drugs at therapeutic concentrations remain to be established. Digitalis, an agent known to have some negative chronotropic effects in many patients, has been reported to be well tolerated in patients with sinus node dysfunction. However, findings in groups of patients do not always relate to individual patients. This report demonstrates a severe toxic effect of a moderate dose of digoxin in a patient with the syndrome of sinus node dysfunction.

Case History
R.L., a 53-year-old American Indian, had mitral valve replacement for isolated mitral regurgitation due to mitral valve prolapse in May, 1972. Although his symptoms of congestive heart failure were relieved by mitral valve replacement, he was maintained on digoxin 0.25 mg/day, postoperatively. During four months of preoperative observation, heart rates ranged between 50 and 60 beats/min. The patient was receiving digoxin 0.25 mg/day during part of this period. Maximum treadmill exercise at this time increased heart rate to only 105 beats/min.

In April, 1973, the patient complained of orthostatic light-headedness. An electrocardiogram demonstrated sinus bradycardia at a rate of 40 beats/min. A nonspecific intraventricular conduction delay was present. There were nonspecific ST-T wave changes that were compatible with digitalis effect.
Digoxin was discontinued and he was hospitalized and monitored. The patient had a history of chronic cough with sputum production. Pulmonary function tests were performed during the previous year. The vital capacity was 4.3 L/min, forced expired volume (1 sec) was 1.55 L/min and maximum mid-expiratory flow was 0.43 L/min. There was no evidence of myxedema. Physical examination showed a thin Indian male in no acute distress with a pulse of 45 beats/min, blood pressure of 125/80, and respiratory rate of 18/min. Cardiovascular examination was unremarkable save for the slow rate and prosthetic valve sounds. Expiratory rhonchi were heard throughout both lung fields. Routine blood chemistries, including electrolytes, were normal. Serum creatinine was 0.8 mg/100 ml. BUN was 14 mg/100 ml. Hemogram and serum LDH were compatible with a mild hemolytic anemia. Serum digoxin was 0.2 ng/ml. Chest X-ray showed low diaphragms and bullous changes in the right lung field. Vectorcardiogram showed terminal superior forces. The mean frontal plane QRS axis was +30°. Continuous electrocardiographic monitoring demonstrated heart rates ranging from 35 to 60 beats/min. The rhythm remained sinus bradycardia. On several occasions sinus pauses in excess of 2.5 sec were noted. There were no episodes of tachyarrhythmia. Five days after admission the patient underwent a three-day protocol of electrophysiologic study.

Electrophysiologic Protocol

Informed consent was obtained and all studies were performed in the resting non sedated, postabsorptive state. On day 1, rate and rhythm were determined from the surface ECG recorded during a 15 minute control period, and during and after infusion of isoproterenol. Isoproterenol infusion rates were increased in 0.005 mcg/kg/min increments every 5 min until an infusion rate of 0.04 mcg/kg/min was achieved. Rate was determined from records obtained during the last minute of the control period and during the last minute of each infusion period. Isoproterenol infusion was then discontinued. After the heart rate returned to the control state, four doses of atropine sulfate 0.005 mcg/kg were given at 5 min intervals. Heart rate was determined from records obtained during the last minute of the control period and during the last minute of each infusion period.

On day 2, under fluoroscopic control, a #6F quadripolar electrode catheter was inserted via an antecubital vein and positioned in the right atrium such that the proximal electrode pair was at the junction of the right atrium and superior vena cava. The proximal electrode pair was used to pace the atrium. The distal pair was used to record the high right atrial electrogram. A #6F tripolectrode catheter was inserted via the right femoral vein and positioned across the tricuspid valve for recording of the His bundle electrogram. Signals from the atrial and His bundle electrodes were simultaneously recorded with the body surface ECG. These signals, along with one second time marks, were simultaneously displayed on a Hewlett-Packard multichannel oscillograph and recorded on FM magnetic tape at 33 inches per second. Records for analysis were obtained by playback to an Elema Mingograf 800 Recorder at paper speeds of 100 and 200 mm/sec. All intervals were measured using a Science Accessories Corporation graf/pen connected to a Digital Equipment corporation PDP-11 computer.

Control recordings of spontaneous sinus rhythm were obtained for a period of 15 minutes. Thereafter, premature atrial stimuli were introduced via the stimulating electrode pair during spontaneous sinus rhythm. The atrial electrogram was used to initiate a programmable stimulator. In this way, atrial premature stimuli — 2–2.5 x diastolic threshold, 2 msec in duration — were introduced via an isolation transformer after every sixth spontaneous sinus cycle. Stimuli were introduced late in atrial diastole and moved progressively earlier in 5–10 msec increments until the entire diastolic period was scanned. Refractory periods were measured during spontaneous sinus rhythm. Overdrive atrial pacing was then performed at various cycle lengths, ranging from 1000–353 msec. Control cycle lengths were obtained during a 5 min period before overdrive was begun. Pacing at each cycle length was continued one minute. Following cessation of pacing, the first 20 cycles were recorded. At completion of the day 2 study, the His bundle catheter was removed and the quadripolar catheter was left in place.

Between days 2 and 3 the patient was given intravenous digoxin. A total dose of 1.025 mg (0.02 mg/kg) was administered in five divided doses over a 24-hour period. The last dose (0.125 mg) was administered two hours prior to electrophysiologic study.

On day 3, control recording, premature atrial stimulation, and overdrive pacing were repeated in a manner identical to that of day 2. Following this, atropine sulfate was administered in four aliquots of 0.005 mcg/kg and the effects on heart rate and escape cycles following overdrive pacing were observed. Isoproterenol was then administered intravenously at incremental infusion rates until a maximum infusion rate of 0.04 mcg/kg/min was achieved. The effects on heart rate and escape cycles following overdrive pacing were observed. At completion of the protocol, the atrial pacing catheter was left in place an additional 18 hours.

Results of Electrophysiologic Study

Days 1 and 2 (Control)

During both study days, the patient manifested a consistent sinus bradycardia. On day 1, the mean cycle length was 1317 msec (table 1). In response to a graded infusion of isoproterenol, the mean cycle length decreased to 546 msec at an infusion rate of 2 mcg/min (table 1). Atropine, 0.02 mg/kg, had no significant effect on heart rate (table 1).

On day 2, the mean value of the A-A interval was 1193 ± 14.0 msec (N = 10); A-H interval was 138 ± 3.9 msec (N = 10); H-V interval 45 ± 4.4 msec (N = 10). The P wave duration was 94 ± 4.2 msec (N = 10), and the QRS complex duration was 118 ± 4.5 msec (N = 10). The QRS configuration was compatible with a nonspecific incomplete intraventricular conduction delay. The functional refractory period (FRP) of the atroventricular node (AVN) was 425 msec at a basic cycle length of 1187 msec. The FRP of the His-Purkinje system was 550 msec at a basic cycle length of 1262 msec. The effective refractory period (ERP) of the AVN was 420 msec at a basic cycle length of 1225 msec. The ERP of the His-Purkinje system was 478 msec at a basic cycle length of 1195 msec.

The effect of premature atrial stimulation is shown in the left hand panel of figure 1. The return and post
Table 1

Summary of Cycle Lengths Observed During Electrophysiological Studies

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Isoproterenol (meg/min) (N = 30)</th>
<th>Day 1</th>
<th>Day 3 (after digoxin, 1.125 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(0.26)</td>
<td>(0.52)</td>
<td>(0.78)</td>
</tr>
<tr>
<td>Mean</td>
<td>1317</td>
<td>1358</td>
<td>1103</td>
<td>941</td>
</tr>
<tr>
<td>sd</td>
<td>68.5</td>
<td>49.5</td>
<td>22.6</td>
<td>32.7</td>
</tr>
<tr>
<td>Range</td>
<td>(1256-1463)</td>
<td>1305-1522</td>
<td>1065-1148</td>
<td>871-978</td>
</tr>
<tr>
<td>% Δ</td>
<td>1317</td>
<td>+3.1</td>
<td>-16.3</td>
<td>-37.5</td>
</tr>
<tr>
<td>Mean</td>
<td>1322</td>
<td>-</td>
<td>1273</td>
<td>1154</td>
</tr>
<tr>
<td>sd</td>
<td>12.5</td>
<td>-</td>
<td>19.1</td>
<td>15.8</td>
</tr>
<tr>
<td>Range</td>
<td>1291-1338</td>
<td>-</td>
<td>1238-1315</td>
<td>-</td>
</tr>
<tr>
<td>% Δ</td>
<td>1291-1338</td>
<td>-3.7</td>
<td>-12.7</td>
<td>-12.7</td>
</tr>
</tbody>
</table>

N = number of observations.

Return cycles are plotted as a function of the test or premature cycle as previously described. Although atrial premature depolarizations at long coupling intervals were not elicited, the responses fall into two zones: a late Zone (I) where return cycles are compensatory and an earlier Zone (II) where return

Figure 1

Results of premature atrial stimulation before (left hand panel) and after (right hand panel) digoxin administration. The return cycles (unfilled circles) and post return cycles (filled circles) are plotted as a function of the test cycles, according to the method previously described. The return cycle, deviation from the line indicating compensatory response is seen to occur at 84.6% of the atrial cycle. After 1.125 mg of digoxin over 24 hr (right panel), the plateau responses are seen to be comparable to those shown in the left hand panel. However, return cycles following late test depolarizations are seen to fall below the compensatory line. These responses would indicate that following digoxin the late test depolarisations induced marked shortening of the sinus return cycle prior to sinus node capture. If earlier test depolarizations also shortened the sinus return cycle, then the plateau return cycle would also be shortened.
DIGITALIS AND SSS

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DIGITALIS cycles are less than compensatory.\textsuperscript{10, 11} The transition between I and II may approximate the sinoatrial conduction time.\textsuperscript{12} This transition occurred at 84.6\% of the atrial diastolic interval (mean A-A interval, 1190 msec), suggesting that the sinoatrial conduction time was not markedly prolonged.

The effect of overdrive suppression at various cycle lengths is shown in figure 2. At pacing cycle lengths of 667, 545, and 462 msec, the escape cycle lengths were not prolonged. At pacing cycle lengths of 400 and 353 msec, abnormal responses were obtained. For example, following a pacing cycle of 353 msec, the first four escape cycles were 1339, 1092, 1492 and 788 msec. The first three intervals are compatible with 5:3 exit block from a pacemaker beating at a cycle length of 785 msec, a value that is very close to the value of the fourth cycle. However, the maximum values of the escape cycles are within normal limits.\textsuperscript{13-15}

In summary, the only abnormalities which could be demonstrated by this extensive electrophysiologic study were sinus bradycardia, "sinus pauses" induced by overdrive, and a failure to respond to atropine administration.

Day 3 (Post Digoxin)

On day 3 (following administration of digoxin, 1.025 mg, over 24 hr), the mean sinus cycle length was 1341 msec (45 beats/min). This was not appreciably different than the control cycle length recorded on day 1. The response to premature atrial stimulation is shown in figure 1. The Zone I right hand panel of figure 1. The Zone I return cycle lengths were similar to those recorded under control conditions. Sinus pauses ranging between 2282 and 3500 msec were noted on five different occasions during the period of premature atrial stimulation. The FRP of the atrioventricular conduction system was 588 msec at a basic cycle length of 1296 msec. The ERP of the atrioventricular conduction system was 525 msec at a basic cycle length of 1251 msec.

Overdrive suppression, on day 3, demonstrated marked abnormalities that were not present on day 2. Figure 3 demonstrates the response to overdrive suppression at a pacing cycle length of 545 msec under control conditions (day 2) and following digoxin (day 3). The escape cycles which were unremarkable under control conditions were dramatically altered on day 3. The first, second, seventh, and ninth cycles were 4748, 4822, 3015, and 2818 msec, respectively. These values are approximately whole number multiples of the third, eighth, and tenth cycles. A more dramatic response is seen in figure 4, in which a 6030 msec pause (second cycle) was recorded on day 3. During this pause the patient complained of slight drowsiness. Figure 5 shows a similar marked prolongation of the sinus escape cycles after pacing at a cycle length of 462 msec. The prolonged sinus pauses persisted for as long as 20 cycles following termination of pacing (fig. 3). The patient did not have any symptoms during these pauses, as a slow A-V junctional escape rhythm without atrial capture occurred concurrently with the abnormal sinus rhythm.

Pauses were seen at pacing cycles as long as 1000 msec. The pauses seen were compatible with sinoatrial exit block.

Atropine, 0.02 mg/kg, was given and no effect on

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Effect of overdrive pacing in the control state. Three representative pacing cycle lengths — 462 msec, 400 msec, and 353 msec — are depicted. The shaded bars represent the mean and the lines associated with each bar represent ±1 SD of ten spontaneous sinus cycles immediately prior to onset of pacing at each cycle length. The numbered bars represent the cycle lengths of successive atrial beats following cessation of pacing. The responses to pacing at cycle lengths of 400 msec and 353 msec are borderline normal.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Effect of digoxin on response to overdrive pacing at a cycle length of 545 msec. The shaded bars and lines represent the mean ±1 SD of ten spontaneous sinus cycles immediately prior to onset of pacing. The numbered bars represent the cycle lengths of successive beats following cessation of pacing. The left hand panel depicts the response at a time when the patient was receiving no medication. The right hand panel depicts the response following the intravenous administration of digoxin, 1.025 mg, over 24 hr. Before digoxin, overdrive pacing at this cycle length had no effect on the spontaneous sinus cycle length. Following digoxin, there was a markedly abnormal response with two consecutive sinus pauses in excess of four seconds. Evidence of "sinus pauses" was still present after 20 spontaneous sinus beats.}
\end{figure}

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Effect of digoxin, and digoxin plus atropine, on response to overdrive pacing at a cycle length of 667 msec. The shaded bars represent the mean ± 1 so of ten consecutive sinus cycles immediately prior to onset of pacing. The numbered bars represent the cycle lengths of successive beats following cessation of pacing. The left hand panel depicts the response at a time when the patient was receiving no medication. The middle panel depicts the response following the intravenous administration of digoxin, 1.125 mg, over 24 hr. The right hand panel depicts the post-digoxin response following the intravenous administration of atropine, 0.02 mg/kg.

Effect of digoxin and digoxin plus atropine and isoproterenol on response to overdrive pacing at a cycle length of 462 msec. The shaded bars represent the mean ± 1 so of ten consecutive sinus cycles immediately prior to onset of pacing. The numbered bars represent the cycle lengths of successive beats following cessation of pacing. The left hand panel depicts the response at a time when the patient was receiving no medication. The middle panel depicts the response following the intravenous administration of digoxin, 1.125 mg, over 24 hrs. The right hand panel depicts the post-digoxin response following the intravenous administration of atropine, 0.02 mg/kg, and during intravenous infusion of isoproterenol, 2 mcg/min. Before digoxin, overdrive pacing at this cycle length had no effect on the spontaneous sinus cycle length. Following digoxin, there was a markedly abnormal response. During isoproterenol infusion, the abnormal response was abolished.

The FRP of the atrioventricular conduction system decreased to 540 msec at a basic sinus cycle length of 1385 msec. The response to overdrive suppression was not appreciably altered by atropine (fig. 4) at pacing cycle lengths ranging between 545 and 1200 msec. Infusion of graded doses of isoproterenol resulted in a decrease in cycle length to a mean value that was comparable with that seen under control conditions. But at each of the three lower infusion rates the mean value of the cycle length was consistently more than that obtained under control conditions (table 1). The abnormal response to rapid atrial pacing following digoxin was completely reversed following exposure to isoproterenol, 2.0 mcg/min (fig. 5). The effects of atropine and isoproterenol on the post-digoxin response to overdrive were consistent at all pacing cycle lengths.

Subsequent Course

Digoxin therapy was discontinued. It was decided not to implant a permanent pacemaker in this patient. He was discharged on warfarin sodium and was instructed to take no other medication. He had no cardiovascular symptoms during the next eleven months. Orthostatic lightheadedness was no longer present. In March, 1974, he began experiencing frequent episodes of rapid irregular palpitations which would abate spontaneously. Later in March, the patient ex-
experienced a prolonged episode of palpitations; syncope and death occurred while the patient was en route to the hospital. No autopsy was obtained.

Discussion

Summary of Findings

This patient presented with clinical evidence of sick sinus syndrome — manifested by sinus bradycardia, a blunted chronotropic response to exercise, spontaneous sinus pauses, and symptoms which could be attributed to bradyarrhythmia. He was on a common maintenance dose of digoxin at the time. During electrophysiologic study in the absence of any digitalis glycoside no definite abnormality of sinus node function could be elicited — even with provocative pacing techniques. Following the administration of only a moderate amount of digoxin, overdrive pacing elicited a strikingly abnormal response. The patient was discharged off digitalis with apparent clinical improvement. This improvement, however, was only temporary. Symptoms returned in less than a year and led to the patient’s untimely death. Whether this clinical deterioration was due to the consequences of sick sinus syndrome and whether it could have been prevented by a prophylactic pacemaker is a matter of speculation.

Mechanism of Digitalis Toxicity in Sick Sinus Syndrome

Because digitalis acts not only upon heart muscle but also upon peripheral smooth muscle and the nervous system, it is sometimes difficult to delineate the pharmacologic and toxic actions of the drug on isolated functions. The effect of digitalis glycosides on heart rate have been shown to be mediated through direct effects on sinus automaticity, control of cardiac decompensation, and effects mediated through autonomic pathways. Most commonly, slowing of the sinus rate following digitalis administration results from the control of congestive heart failure. When usual clinical doses of digitalis are administered to normal man, there is little if any change in sinus rate. Relatively large doses of digitalis administered to experimental animals do tend to cause sinus slowing. However, this effect appears to be mediated predominantly through the autonomic nervous system. These autonomic effects appear to include both enhancement of vagal tone and antagonism of adrenergic input.

In this patient part of the effect of digitalis on sinus node function appeared to have been mediated through the autonomic nervous system. The long sinus pauses induced by overdrive pacing in the presence of digoxin were only slightly shortened by atropine. However, atropine may have a paradoxical effect on sinus pauses following rapid atrial pacing in some patients with sinus node dysfunction, and the effects obtained in our patient are difficult to interpret in that light. The additional infusion of isoproterenol entirely reversed the abnormalities caused by digoxin. Isoproterenol’s rather dramatic effect in reversing these abnormalities suggests that it may improve depressed conduction as well as increase automaticity. However, at the time of administration of isoproterenol, therapeutic doses of atropine had already been given. It is possible that this complete reversal of digitalis toxicity might have occurred only in the presence of both isoproterenol and atropine.

The mechanism of sinus node dysfunction in this patient is uncertain. The extremely long pauses suggest a possible role for sinoatrial block. In the middle panel of figure 5 the cycle lengths for beats 1, 2 and 5 are, respectively, four times, four times, and two times the value of the third and sixth cycles. This lends additional credence to the possibility of an exit block mechanism. The long pauses illustrated in figure 2 are compatible with 5:3 exit block. Pauses which occurred spontaneously during the period of premature atrial stimulation were also seen. Whether these long pauses reflected the sinoatrial block that has been associated with digitalis toxicity or sub-threshold oscillations in sinoatrial node transmembrane potentials or disturbance of pacemaker current is unknown. It is of interest that the results obtained using the prematurity atrial stimulation technique do not suggest a markedly prolonged sinoatrial conduction time.

Meaning of Electrophysiologic Findings

Because access to the sinoatrial node, particularly in man, is impossible, any method used to study sinus node function is of necessity inferential. Until recently, delineation of disorders of sinus node function in man has been limited to deductive analysis of the surface electrocardiogram. During the past several years intracardiac electrode recording and pacing studies have increased our awareness of the scope of sinus node dysfunction in man. Although these techniques have allowed us to study patients in detail, we do not yet have sufficient experience with them to make meaningful prognostic and therapeutic decisions.

Overdrive pacing, which has been shown to suppress cardiac pacemaking tissue, has been advocated as a means of provoking sinus dysfunction in patients with sick sinus syndrome. Following overdrive pacing, normal subjects respond with a moderate prolongation of the spontaneous sinus cycle length, followed by a brief "warm-up" resulting in progressively shorter cycle lengths, and then continue at their previous sinus rate. The usual response to overdrive in sick sinus syndrome is a marked
prolongation of the initial spontaneous sinus cycle, followed by a prolonged warm-up period, and finally the resumption of the previous sinus rate. Unfortunately, there is considerable overlap in the responses of normal subjects with those of patients with sick sinus syndrome. When sick sinus syndrome results from exit block of the sinus impulse, there may be a considerable entrance block to the overdrive stimulus. This may lead either to no suppression of sinus pacemaker activity and normal escape intervals or to exaggeration of exit block with prolonged pauses. This might have been the phenomenon which occurred in this patient.

Programmed premature atrial stimulation has been recently advocated as a useful adjunct to the study of sinus node function in man. Strauss et al. have suggested that this technique may permit indirect measurement of sinoatrial conduction time. However, recent studies in rabbits have shown that this method cannot accurately measure sinoatrial conduction time. Whether these latter results are applicable to the clinical studies of sinus node function is uncertain, but in this patient the results obtained with the use of rapid atrial pacing were more helpful.

The routine evaluation of patients with sinus node dysfunction in the absence of a pharmacologic challenge may lead one to conclude that a patient has no significant disease or that the tests are of limited functional value in the evaluation of patients. Electrophysiologic study of this patient before and after digoxin administration demonstrates the extent of sinus node dysfunction induced by a therapeutic dose of digoxin. However, the results obtained during ambulatory monitoring shortly after admission to hospital, while the patient was excreting his digoxin, provided qualitatively similar information.

Clinical Implications

Although extraordinarily useful in the treatment of a myriad of cardiac disorders, digitalis preparations have been demonstrated to cause many different toxic symptoms and signs, some of which can be serious or lethal. Clinicians must be constantly aware of possible toxic manifestations of this drug. Serum digoxin levels may be useful in defining a setting in which toxicity is likely to occur, but toxic manifestations may occur even at serum concentrations well within the therapeutic range. This was true with this patient.

The experience of other authors suggests that there is no absolute contraindication to digitalis therapy in patients with sick sinus syndrome. However, it is evident that even small amounts of this agent may be extremely toxic for selected patients. Digitalis preparations should be used with caution in patients with sick sinus syndrome. When such patients must be treated, it is prudent to observe them carefully with continuous electrocardiographic monitoring in the presence of full therapeutic drug levels. If there is any evidence that digitalis provokes the manifestations of sick sinus syndrome and its continued usage is mandatory, then prophylactic permanent pacemaker therapy should be considered.

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