DISOPYRAMIDE, a recently introduced antiarrhythmic agent, is effective in treating several ventricular and supraventricular arrhythmias.1-11 The electrophysiologic effects of this drug are similar to quinidine, and might result in depression of sinus node function caused by direct membrane depressant effects.12, 13 In contrast, the atropine-like effects of disopyramide are reportedly responsible for shortening the spontaneous cycle length and the sinus node recovery time.14-16 Since the drug decreased spontaneous cycle length and sinus node recovery time, Befeler et al.18 suggested that it might be particularly useful in the treatment of arrhythmias in patients who had slow sinus rates. However, Seipel et al.19 reported that in four patients with sick sinus syndrome, disopyramide significantly depressed sinus node recovery time, and therefore recommended it not be used for such patients. Systematic evaluation of the electrophysiologic effects of this agent in a large cohort of patients with sinus node disease is not available. This study was therefore undertaken to determine the electrophysiologic effects of disopyramide in a large group of patients with sinus node dysfunction.

Methods

Sixteen consecutive patients suspected of having sinus node dysfunction on the basis of sinus bradycardia (heart rate less than 60 beats/min), sinoatrial block, sinus pauses or episodes of supraventricular tachyarrhythmias alternating with sinus bradycardia were studied in the clinical electrophysiology laboratory. Medical history, physical examination and written informed consent were obtained on each patient before study. Patients with acute pulmonary edema, uncontrolled congestive heart failure, cardiogenic shock, glaucoma, hyperthyroidism or urinary retention were excluded from the study. Patients were in a resting, non-sedated, postabsorptive state and were in sinus rhythm at the time of study.

On the first day leads I, II, III and V_{1} of the surface ECG and 100 msec time marks were simultaneously recorded on FM magnetic tape (3-3/4 IPS) and on an Elema Mingograph 800 recorder and displayed on a Hewlett Packard multichannel oscilloscope. Ten minutes were allowed for equilibration, and near the end of this period 20 spontaneous cycles were recorded as a control. Four 0.005 mg/kg aliquots of atropine sulfate were administered at 5-minute intervals, and 20 cycles were recorded 4 minutes after each aliquot.

On the second day patients returned to the electrophysiology laboratory. In addition to surface ECGs, high right atrial and His bundle electrograms were obtained with two intracavitary electrodes. Procaine 2\% was used as local anesthetic. A \#6 French quadripolar...
electrode catheter (interelectrode distance 1 cm) was passed percutaneously into the femoral vein. The tip of the catheter was advanced to the junction of the superior vena cava and the right atrium under fluoroscopic control. The proximal pair of electrodes were used to record the atrial electrogram and the distal pair were used to stimulate the right atrium. A #6 French tripolar electrode catheter was similarly placed and advanced to lie across the tricuspid valve to record the His bundle electrogram. Filter settings for the atrial electrogram recordings were 4–1000 Hz and for the His bundle recordings, 50–1000 Hz. After a 15–20-minute stabilization period we obtained control recordings and measured spontaneous cycle length (A-A), P-wave duration, P-R interval, QRS duration, QT interval, A-H and H-V intervals.

The premature atrial stimulation technique was carried out as previously described. Premature stimuli of 2–4 msec duration and 2–4 mA intensity were delivered through the atrial intracavitary electrode after every eighth spontaneous sinus cycle. The premature stimulus was moved in 5–10 msec decrements throughout the atrial diastolic interval. Spontaneous cycle length (A1A1 interval), premature cycle length (A1A2), atrial return cycle length (A2A3) and atrial post-return cycle length (A3A4) were measured. The atrial return cycle (A2A3) normalized by the spontaneous cycle (A1A1) was plotted against the premature cycle (A1A2) also normalized by A1A1.

All premature cycles (A1A2) which were followed by compensatory atrial return cycles (A2A3) such that A1A2 + A2A3 = 2A1A1 were designated zone I. Less-than-compensatory sets (A1A2 + A2A3 < 2A1A1) were designated zone II. Points which fell in the latest third of zone II were used to calculate the sinoatrial conduction time (SACT) using the formula A2A3 − A1A1 = SACTA+R. SACT was considered to be abnormally prolonged if it exceeded 206 msec.

The response to rapid atrial pacing was analyzed as previously described. Twenty spontaneous cycles were recorded as a control. The atrium was then paced for 1-minute periods at cycle lengths of 860, 660, 540, 460, 400 or 353 msec (corresponding to heart rates of 70, 90, 110, 130, 150 or 170 beats/min, respectively). Pacing was carried out three times at each cycle length. The ECG was closely monitored during this time to ensure complete atrial capture. A-H and H-V intervals were also measured. After 60 seconds of pacing, the stimuli were abruptly stopped and the first 10 spontaneous cycles were recorded. The first post-pacing cycle duration was measured and maximum first post-pacing cycle length was noted. The first post-pacing cycle was considered to be prolonged if it exceeded the values shown by Benditt et al. (table 1).

Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Electrophysiologic data</th>
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<td>A-A SACT SNRTmax 2P</td>
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<td>JK</td>
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<td>LC</td>
<td>Mod - I − −</td>
<td>771 191 1527 +</td>
<td>801 149 1347</td>
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Group A—Patients with sinus pauses and/or sinoatrial block. Group B—patients with sinus bradycardia.

Control - Sinus Bradycardia (SB): considered severe (S) if heart rate < 40, moderate (Mod) 40–49, minimal (min) 50–59. I = intermittent, P = persistent, NP = not performed. Patients with abnormally prolonged sinus pauses (SP), sinoatrial exit block (SAB) or secondary pauses (2P) are indicated by +. Abnormal responses are underlined.

*SACTA+R not evaluated since patient developed atrial fibrillation during premature atrial stimulation.

†SACTA+R not evaluated since marked change in P wave configuration occurred 15 min following disopyramide administration.
The functional refractory period of the atrium and atrioventricular node were evaluated by the atrial extrastimulus method. A basic pacing cycle length (S1S1) of 600 or 660 msec was used. Premature stimuli (S1S2) were introduced after every eighth beat. The premature stimulus was moved in 5–10 msec decrements throughout the atrial diastolic interval until S2 failed to elicit an A2. The shortest A1A2 interval was measured to determine the atrial functional refractory period. The shortest H1H2 interval was measured to determine the atrioventricular nodal functional refractory period.

The patient was then given 2 mg/kg of disopyramide phosphate intravenously over a 3–5-minute period, and all electrophysiologic testing was repeated beginning 5 minutes after completion of the infusion. Blood samples were drawn for determination of plasma concentration of disopyramide phosphate at 5, 10 and 40 minutes after administration.

Data are expressed as the mean ± SD. Statistical analysis was performed using the t test for paired data. The correlation between two variables was examined using a linear regression model.

Results

The patient population included nine male and seven female patients (mean age 58 ± 14 years). Patients had a variety of symptoms: eight experienced syncope, five dizziness and three seizures. Six patients experienced chest pain and three dyspnea. Seven patients had radiographic evidence of cardiac enlarge-ment. Etiology of heart disease was considered to be atherosclerosis in six patients, hypertension in three and rheumatic heart disease in one. Two patients had previous open heart surgery, one had ventricular septal defect repair and one mitral valve replacement. Etiology could not be determined in nine patients. Routine ECGs demonstrated sinus bradycardia in 11 patients, sinus pauses in two and sinoatrial block in one. Seven patients had first-degree atrioventricular block, and three had intraventricular conduction disturbances (two right bundle branch block and one left bundle branch block). Ambulatory electrocardiographic monitoring revealed that seven patients had sinus pauses; in five patients these were abnormally prolonged, exceeding 1.7 sec (waking hours) or 2 sec (sleeping hours). Three patients had sinoatrial block, and five had atrial arrhythmias (table 1). Permanent intracardiac artificial pacemaker systems were implanted in 11 of 16 patients.

The patients were subdivided into two groups: group A, those with sinus pauses and/or sinoatrial block with or without sinus bradycardia (n = 8); and group B, those with only sinus bradycardia (n = 8).

Plasma concentrations of disopyramide during the study were 3.8 ± 0.8 µg/ml at 5 minutes, 3.2 ± 1.2 µg/ml at 10 minutes and 2.6 ± 0.7 µg/ml 40 minutes after administration. Electrophysiologic studies began approximately 5 minutes after administration and were complete within 45–50 minutes. In 12 of 16 patients, the 40-minute plasma concentration of disopyramide was in the therapeutic range (2–4 µg/ml).

**Figure 1.** Effects of disopyramide on spontaneous cycle length: 10 of 16 patients had decreased mean A-A, consistent with atropine-like effects. One patient in group A (MB) had a dramatic increase of 91% after a period of sinus arrest with an escape atrioventricular junctional rhythm. One patient in group A (JK) had a dramatic decrease of 51% due to the disappearance of the 2:1 sinoatrial exit block.
Effects on Sinus Node Function

Spontaneous Cycle Length

Five of the 16 patients had spontaneous cycle lengths longer than 1000 msec under control conditions. Disopyramide shortened spontaneous cycle length (A-A) in 10 of 16 patients (fig. 1) and lengthened A-A in six patients (table 1). The mean cycle length changed from 1012 ± 372 msec to 979 ± 273 msec (n = 16, NS). In group A mean A-A changed from 1011 ± 461 msec to 994 ± 347 msec (NS), and in group B mean A-A changed from 1012 ± 289 msec to 963 ± 195 msec (NS). One patient in group A (MB) showed a marked increase in mean A-A of 91% (fig. 2). This patient had a spontaneous cycle length of 904 msec during the control period, but had a few prolonged cycles, averaging 1720 msec. After receiving disopyramide, she had an 18-second sinus pause and an atrioventricular junctional escape rhythm. Thereafter, a sinus rhythm with a mean A-A of 1771 msec appeared and persisted through the rest of the study. One patient in group A (JK) showed a marked decrease in mean cycle length of 51%, presumably the result of an abatement of the 2:1 sinoatrial exit block. Since these patients often had sinus pauses and sinoatrial block before and especially after disopyramide, sinus node cycle length would probably not equal atrial cycle length. To determine the effect of disopyramide on sinus node cycle length, those cycles demonstrating sinus pauses and sinoatrial block were eliminated, and the measurements for the group A patient (MB) discussed above were eliminated entirely. Sinus node cycle length changed from 945 ± 240 to 907 ± 181 msec (NS) in all patients. In group A patients, the value decreased from 868 ± 154 to 843 ± 153 msec (p < 0.05), and in group B it changed from 1012 ± 289 to 963 ± 195 msec (NS). These changes were consistent with the atropine-like effect of disopyramide.14-16 The effects of disopyramide on spontaneous sinus node cycle length were compared with the effects of atropine. Atropine decreased mean spontaneous sinus node cycle length from 903 ± 185 to 676 ± 169 msec (p < 0.001). In group A it changed from 846 ± 151 to 628 ± 94 msec.

![Figure 2](https://example.com/image2.png)

**Figure 2.** Effect of disopyramide on spontaneous cycle length in patient MB. Control spontaneous cycle length was 904 ± 11 msec (panel A). Two minutes after disopyramide administration (panel B), an 18-second pause in sinus rhythm appeared. During this pause an atrioventricular junctional rhythm (mean cycle length 922 msec) was present. Thereafter, the pauses became shorter and less frequent. Five minutes after disopyramide administration (panel C), the spontaneous sinus cycle length was 1727 ± 52 msec and an atrioventricular junctional rhythm with interference appeared. In addition, QRS duration increased from 141 msec (panel A) to 188 msec (panel C) after disopyramide administration. Plasma concentration of disopyramide was 3.2 μg/ml 5 minutes after administration. HRA = high right atrial electrogram; HBE = His bundle electrogram.
Effects of disopyramide and atropine on spontaneous cycle length: Disopyramide (2 mg/kg) shortened spontaneous cycle length (A-A) in 11 of 15 patients and atropine (0.02 mg/kg) shortened A-A in 14 of 15 patients (p < 0.001). One patient, MB, developed 2:1 block and was not included. Disopyramide was less effective than atropine in changing spontaneous cycle length. SAN = sinus node.

Estimated Sinoatrial Conduction Time

Estimated SACT ($SACT_{A+R}$) was abnormally prolonged (greater than 206 msec) in seven of 15 patients under control conditions. $SACT_{A+R}$ could not be measured both before and after disopyramide in two patients (table 1). After administration of disopyramide, $SACT_{A+R}$ decreased in seven of 14 patients and increased in seven patients (table 1). Mean value for the group as a whole changed from $188 \pm 60$ to $191 \pm 74$ msec ($n = 12$), but this was not significant. In group A patients the mean $SACT_{A+R}$ changed from $234 \pm 40$ to $235 \pm 66$ msec (NS) and in group B patients from $165 \pm 56$ to $168 \pm 70$ msec (NS). One

Figure 3. Effects of disopyramide and atropine on spontaneous cycle length: Disopyramide (2 mg/kg) shortened spontaneous cycle length (A-A) in 11 of 15 patients and atropine (0.02 mg/kg) shortened A-A in 14 of 15 patients (p < 0.001). One patient, MB, developed 2:1 block and was not included. Disopyramide was less effective than atropine in changing spontaneous cycle length. SAN = sinus node.

Figure 4. Sinoatrial conduction time ($SACT_{A+R}$) in patient MB. $SACT_{A+R}$ decreased from 278 to 138 msec after disopyramide and was associated with a change in spontaneous cycle length from 926 to 1720 msec, and is probably due to development of 2:1 sinoatrial exit block.
patient in group A (MB) showed a large decrease in SACT, from 278 to 138 msec, which was associated with a change in spontaneous cycle length from 926 to 1720 msec (fig. 4). This change was probably due to the development of 2:1 sinoatrial block after disopyramide (table 1) and is comparable to changes in atrioventricular conduction time occurring during the transition from first to second degree atrioventricular block during shift of an atrial pacemaker site to a more proximal site. Another group A patient (MS) showed progression of first-degree to second-degree sinoatrial block after disopyramide. A third group A patient (KL) in whom SACTA + R was not measured under control conditions had second-degree sinoatrial block after disopyramide.

**Sinus Node Recovery Time**

The effects of disopyramide on maximum first post-pacing cycle are shown in figure 5. Maximum first post-pacing cycle length decreased in five of 16 patients and increased in 11 of 16 patients (table 1). The mean and range of values of the maximum first post-pacing cycle length for the group as a whole changed from 2360 (988–6315) to 4749 (996–40680) msec (NS). In group A patients the mean value changed from 3251 to 7955 msec, and in group B it changed from 1470 to 1543 msec; none of these changes were significant. Four group A patients (AG, MS, MB and KL) had marked changes in maximum first post-pacing cycle length. Three had increases of 81%, 329%, and 544%, and one had a decrease of 73%.

In general, group A patients had larger mean changes in normalized first post-pacing cycles than group B patients (fig. 6). The group A patients also showed more variability in normalized post-pacing cycle length after disopyramide administration. There was no correlation between changes in post-pacing cycle length and plasma levels of disopyramide. Secondary pauses were present under control conditions in 10 of 16 patients. Four of these patients had fewer pauses after disopyramide.

**Effects on Atrial, Atrioventricular Nodal and Infranodal Conduction and Refractoriness**

The number of patients with prolonged complexes or intervals under control conditions were as follows: 11 of 16 had P waves longer than 120 msec, six of 16 had PR intervals longer than 210 msec, three of 16 had QRS durations longer than 120 msec, four of 15 (one patient did not have a His bundle electrogram recorded) had A-H intervals exceeding 130 msec and three of 15 had H-V intervals longer than 55 msec. The effect of disopyramide on the duration of the complexes or intervals during spontaneous rhythm is shown in figure 7. The duration of the P wave increased in 14 of 15 patients (in one patient P waves could not be accurately measured), from 128 ± 12 to 145 ± 22 msec (p < 0.001). The one patient whose P wave duration decreased as a result of disopyramide also had a marked change in P wave configuration. The duration of the P-R interval increased from 201 ± 47 to 214 ± 54 msec (14 of 16 increased,
FIGURE 6. Changes in first post-pacing cycle normalized by mean value of spontaneous cycle length. Group A patients with sinoatrial block and/or sinus pauses had larger mean changes and more variability in post-pacing cycle length after disopyramide than group B patients with sinus bradycardia. Example: group A (MS) — SCL control = 1144 msec; SCL disopyramide = 1194 msec. Example: group B (GM) — SCL control = 924 msec; SCL disopyramide = 863 msec.

$P < 0.025$). A-H intervals did not change significantly; they increased in nine patients, decreased in five and were unchanged in one. The duration of the H-V interval increased from $47 \pm 11$ to $55 \pm 14$ msec (12 of 15 increased, $P < 0.005$). The QRS interval was prolonged in all patients, from $112 \pm 22$ to $126 \pm 30$ msec ($P < 0.001$). There was no correlation between plasma levels of disopyramide and magnitude of changes in spontaneous cycle length, P wave or QRS durations or P-R, A-H, or H-V intervals.

Functional refractory period of the atrioventricular node, functional refractory period of the atrium, and A-H interval were determined at a basic cycle length of 600 or 660 msec. (fig. 8). The A-H interval decreased in nine and increased in three. In three patients the A-H interval at this basic cycle length could not be measured due to block in the atrioventricular node, and in one patient His bundle recordings were not obtained. The mean value changed from $134 \pm 44$ to $134 \pm 54$ msec (NS). The functional refractory period of the atrioventricular node increased in seven patients and decreased in five. In three patients the functional refractory period of the atrioventricular node could not be measured at this basic cycle length due to second degree atrioventricular block, and in one patient His bundle recordings were not obtained. The mean value changed from $444 \pm 72$ to $450 \pm 56$ msec (NS). Atrial functional refractory period increased in 10 patients and decreased in four, and was not measured in two patients. The mean value changed from $281 \pm 61$ to $304 \pm 57$ msec ($P < 0.01$).

Two patients who had atrial fibrillation during premature atrial stimulation and one who had atrial fibrillation during rapid atrial pacing did not have this arrhythmia after disopyramide. However, two other patients developed atrial fibrillation during rapid atrial pacing after disopyramide. One patient who had multiple atrial premature depolarizations during premature atrial stimulation under control conditions did not demonstrate this arrhythmia after disopyramide.

**Discussion**

Disopyramide is an antiarrhythmic agent with electrophysiologic effects similar to quinidine.$^{12, 13}$ In in vitro experiments performed on superfused Purkinje fibers, disopyramide decreased the maximum diastolic potential and phase 0 amplitude, depressed membrane responsiveness and slowed conduction.$^{12, 13}$ Disopyramide increased the duration of the action potential and prolonged the functional refractory period.$^{12, 13}$ Disopyramide has also been shown to decrease the slope of phase 4 depolarization, thereby decreasing automaticity. In addition, disopyramide also has some atropine-like effects$^{1}$ which have been used to explain the effects of disopyramide on spontaneous cycle length.$^{14-16, 23}$ The potency of disopyramide compared with atropine was 0.5% in rabbit ileal muscle.$^{1}$ To evaluate the potency of disopyramide compared with atropine on spontaneous cycle length, we compared the chronotropic effects of atropine (0.02 mg/kg I.V.) with those of disopyramide (2
mg/kg I.V.). Atropine was more effective than disopyramide at shortening sinus node cycle length. Not only was this dose of disopyramide less effective than atropine in decreasing spontaneous cycle length, but it also actually increased spontaneous cycle length in six of our patients with sinus node dysfunction. Vismara et al.\textsuperscript{10} found disopyramide decreased spontaneous cycle length in normal patients by 63 ± 67 msec.
Three patients in group A had prolongations of spontaneous cycle lengths that exceeded 71 msec, a value that represents the mean values less 2 standard deviations in the data reported by Vismara et al. In one patient (MB), this was probably due to the development of 2:1 sinoatrial exit block. In another group A patient (JK), however, spontaneous cycle length markedly decreased as a result of disopyramide, probably due to the abatement of 2:1 sinoatrial exit block. In this patient, 30 minutes later there was a marked change in P-wave configuration, suggesting a marked shift in pacemaker site.

Disopyramide decreased estimated antegrade and retrograde SACT in seven patients and resulted in a temporary but marked improvement in the frequency of spontaneous 2:1 sinoatrial exit block. In contrast, disopyramide had markedly depressant effects on sinoatrial conduction in three patients, resulting in the development of second-degree sinoatrial exit block during premature atrial stimulation in two group A patients. In another patient, although the estimated SACT was not determined under control conditions, second-degree sinoatrial exit block during premature atrial stimulation occurred after administration of disopyramide. However, we cannot evaluate the degree of depression of sinoatrial conduction by disopyramide in this patient, since control values were not determined. Probably, the membrane effects, rather than the atropine-like effects of the drug, account for the depression of sinoatrial conduction, since only one of the three patients in whom disopyramide markedly depressed sinoatrial conduction had a positive chronotropic response.

Although Befeler et al. demonstrated that disopyramide decreased sinus node recovery time and suggested that this drug would be safe to use in patients with slow sinus rates, our study suggests that prolongation of sinus node recovery time may occur in many patients with sinus node dysfunction — 11 of 16 in our study. Furthermore, sinus node recovery time was markedly prolonged by disopyramide (longer than 500 msec in four patients), confirming the preliminary findings of Seipel et al., who observed longer sinus node recovery time as a result of disopyramide in four patients with sinus node dysfunction. Seipel et al. suggested that an improvement in retrograde conduction to the sinus node during pacing would permit more impulses to engage the sinus node, causing more overdrive suppression of sinus automaticity on termination of rapid drive. In support of this view, five of seven patients in their study that had decreased estimated SACTs also had an increase in sinus node recovery time. However, in all of the four patients who had very marked increases of sinus node recovery time after disopyramide also had prolonged sinoatrial conduction. Thus, marked prolongation of sinus node recovery time may also be caused by depressed sinoatrial conduction during the post-pacing period.

Regardless of the mechanism, three of four patients with marked prolongation in sinus node recovery time resulting from disopyramide were group A patients. Further, the marked increases in sinus node recovery times occurred in patients who demonstrated secondary pauses under control conditions. Sinus bradycardia, on the other hand, was severe in two patients and was either minimal or absent in the other two. Thus, our study suggests that the ambulatory or resting heart rate may not be suitable for identification of patients at risk for development of prolonged sinus node recovery times after disopyramide, and that the presence of sinus pauses, sinoatrial exit block or secondary pauses after termination of rapid atrial pacing may permit identification of patients who are likely to show these adverse responses to this drug. The drug was well tolerated in group B patients, with minimal or moderate sinus bradycardia.

The extrapolation of our findings from the clinical electrophysiology laboratory to the clinical setting is not entirely justified by this study. However, the four patients demonstrating marked prolongation in sinus node recovery time as a result of disopyramide also had bradycardia exacerated during chronic therapy with α-methyldopa (MB, KL and LC) or digoxin and quinidine (RS). Thus, while not enough patients were studied to draw firm conclusions, we recommend that disopyramide be used cautiously in patients with sinus node dysfunction, in particular patients with sinus pauses, sinoatrial exit block, or secondary pauses after termination of rapid atrial pacing.

The effects of disopyramide on the duration of the P wave, QRS complex and on the A-H and H-V intervals were determined to evaluate the effects of this drug on conduction elsewhere in the heart. Disopyramide significantly increased the duration of the P wave and QRS complexes and the H-V interval, confirming previous observations. The variable effect of disopyramide on atrioventricular nodal conduction, measured by the A-H interval, confirms previous observations. Since the atropine-like effects of disopyramide improved both sinoatrial and atrioventricular nodal conduction, to determine if the magnitude of change in the two nodes were comparable we examined the relationship between the change in A-H interval and estimated SACT caused by disopyramide; no correlation was found. However, three of the five patients whose A-H shortened with disopyramide also had a shortening of SACTA-H.

In summary, the electrophysiologic effects of disopyramide on sinus node function are explained by both direct membrane and atropine-like effects. Intravenous administration was generally well tolerated; however, in a few patients, particularly those with secondary sinus pauses or those with sinus pauses and/or sinoatrial or exit block, marked changes in spontaneous cycle length, sinus node recovery time or SACT occurred. The effects of intravenous disopyramide on these three parameters of sinus node function are similar to those described for propranolol. These observations suggest that disopyramide, as other antiarrhythmic drugs, should be
administered cautiously to patients with sinus node dysfunction, particularly those with sinus pauses and/or sinoatrial exit block or secondary sinus pauses.

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