Plasma Concentration and Urinary Excretion Kinetics of Acetyl Strophanthinidin

By Richard Selden, M.D., Michael D. Klein, M.D., and Thomas W. Smith, M.D.

SUMMARY
The pharmacokinetics of acetyl strophanthinidin (AS) were studied in dogs and human subjects by the use of a newly developed radioimmunoassay. This method has a sensitivity of 0.1 ng of AS per ml and is applicable to direct measurement of AS in unextracted plasma, urine, or bile. After administration of a single intravenous (i.v.) dose of 1.0 mg of AS to 17–25-kg mongrel dogs, the principal exponential decline of plasma AS concentration began 20–60 min after the injection and had a mean half-life (T1/2) of 83 ± 19 min (SD). Mean total urinary excretion of AS was 13.3 ± 4.8% of the i.v. dose and occurred with a mean T1/2 of 79 ± 10 min. Biliary excretion of AS accounted for only 1.5–2.1% of the i.v. dose. After i.v. administration of 1.0 mg of AS to seven human subjects, the principal exponential decline of plasma AS concentration began 10–30 min after the infusion and had a mean T1/2 of 2.3 ± 0.2 hours. Urinary excretion of AS, studied in two patients, accounted for an average of 21.8% of the i.v. dose and occurred with a mean T1/2 of 2.4 hours. Thus the plasma level T1/2 of AS in human subjects is about tenfold shorter than the 22-hour T1/2 previously observed for the relatively short-acting cardiac glycoside ouabain, in agreement with the known brief duration of pharmacologic effects of acetyl strophanthinidin.

Additional Indexing Words:
Digitalis Radioimmunoassay Pharmacokinetics Biliary excretion

ACETYL STROPHANTHIDIN (AS), a synthetic C-3 acetyl ester of the aglycone strophanthinidin, was developed by Chen and Elderfield in 1942. Since then, extensive experimental studies have shown AS to share with the cardiac glycosides the ability to increase myocardial contractility2–5 and to enhance the automaticity of ectopic pacemakers.6–8 AS has also been shown to share with cardiac glycosides the ability to produce potassium loss from myocardial cells9–11 and to increase peripheral vascular resistance.3, 12 Clinically, AS has been used to assess the state of digitalization of acutely ill patients,13–22 to revert various supraventricular tachycardias to normal sinus rhythm,23, 24 and to slow the ventricular response to atrial fibrillation and atrial flutter.25, 26 In both laboratory experimental and clinical studies, the onset of therapeutic and toxic effects has been noted to occur within a few minutes of AS administration.5, 23–26 with peak effects occurring within 5–15 min.3, 5, 23–26 Toxic arrhythmias typically persist for 5–30 min.15–18, 21 Slowing of the ventricular response in patients with atrial fibrillation has been shown to persist for 6–8 hours after single doses of AS.25, 26 dissipating with a half-life of about 80 min. The half-life of dissipation of left ventricular ejection time shortening after AS administration in patients with normal hemodynamics has been estimated at 40 min.27 Dissipation of the (dp/dt)/P increase in closed-chest dogs after AS occurred with a half-life of 17 min.3 Thus, this agent is by far the most rapidly acting digitalis analog which has received extensive clinical and experimental use.

Despite the use of AS for 30 years, no direct pharmacokinetic data have been reported owing to the lack of a means to quantify circulating levels of AS in serum or plasma. We have therefore developed a new technic for the rapid and precise measurement of subnanogram amounts of AS in biologic fluids including plasma, urine, and bile. Using this method, we have studied plasma and urine pharmacokinetics of AS in human subjects and in dogs; biliary excretion has also been assessed in dogs.

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KINETICS OF ACETYL STROPHANTHIDIN

Methods

Acetyl Strophanthidin Radioimmunoassay

Competition between AS and ouabain for antibody-binding sites of antiouabain antibodies was utilized in developing the radioimmunoassay for AS. High-affinity antiouabain antibodies with substantial AS cross-reactivity were raised in rabbits challenged with a conjugate of ouabain coupled through the rhamnose group to terminal ω-amino groups of poly D, L-alanyl human serum albumin.28 One ng of tritiated ouabain (3H-ouabain; specific activity 11.7 Ci/mmmole)* and 50 μliters of a suitable dilution of antiouabain antiserum28 in phosphate-buffered saline (0.15 molar NaCl, 0.01 moles Na₂HPO₄, adjusted to pH 7.4 with H₃PO₄) were added directly to aliquots of plasma, urine, or bile containing unknown amounts of AS. The dilution of antiserum was chosen to provide 35–40% antibody binding of the 1-ng tracer quantity of 3H-ouabain in the absence of any competing ligand. Aliquot sizes ranged from 500 to 1000 μliters for plasma, 10–200 μliters for urine, and 10–50 μliters for bile. Urine and bile aliquots were added to 0.5 ml normal human plasma and sufficient phosphate-buffered saline to provide a total volume of 1.0 ml. Standards were prepared by adding known amounts of AS† to the same volume of control plasma, urine, and/or bile present in unknown samples. Following a 30-min period of equilibration of 3H-ouabain and unlabeled AS with antibody binding sites, activated charcoal coated with molecular weight 80,000 dextran29 was added. Free 3H-ouabain and AS were selectively bound to charcoal and centrifuged, allowing antibody-bound 3H-ouabain to be decanted into a toluene-detergent base scintillation fluid (Instagel)+ and counted in a liquid scintillation spectrometer.4 Quenching variation was corrected by the use of a 226Ra external standard or by the addition of internal standards consisting of the original tracer quantity of 3H-ouabain. AS content of unknown samples was determined by comparison with a simultaneously run standard curve constructed with same AS preparation used in the experimental animals and human subjects. All samples were determined in duplicate.

Specificity of the assay system was determined by testing for displacement of 3H-ouabain from the antibody binding site by a number of endogenous steroid compounds including cholesterol, cortisol, dehydroepiandrosterone, 17-β-estradiol, progesterone, and testosterone in concentrations substantially in excess of those known to occur physiologically. Precision was assessed by determination of agreement between 135 pairs of duplicate samples run in the course of these studies.

Canine Studies

Under intravenous pentobarbital anesthesia, a polyethylene catheter was inserted into the external jugular vein, and Foley catheter into the bladder of four 17–25-kg female mongrels; one of these dogs also underwent common biliary duct ligation and cholecystectomy. Control samples of blood, urine, and bile were then obtained. The day after surgery, each animal received 1.0 mg of AS as an intravenous infusion into a foreleg vein over a period of 30 sec. The jugular venous catheter, kept patent with heparinized saline, was used to obtain blood samples at ½, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 24 hours after the injection. In addition, blood samples were obtained each 5 min during the first half hour after injection in four of the canine experiments. Urine and bile collection periods were from 0 to 2, 2–4, 4–6, 6–8, 8–10, and 10–24 hours after injection. The same experimental protocol was repeated in each animal after an interval of 4–7 days.

Human Studies

Seven subjects were studied. Four were normal, two had paroxysmal atrial fibrillation without other evidence of cardiac disease, and one had documented coronary artery disease. None was receiving digitalis medication at the time of this study. As indicated in table 1, renal function and electrolytes were normal in each subject. After obtaining fully informed consent, AS was administered as an intravenous infusion. Six subjects received 1.0 mg over an interval of 10 min and one subject received 1.5 mg over an interval of 25 min. Continuous electrocardiographic monitoring did not show any changes of digitalis intoxication in any subject. Blood samples were subsequently obtained.

*New England Nuclear Corp., Boston, Massachusetts.
†Supplied by Dr. G. C. Chiu, Eli Lilly Co., Indianapolis, Indiana.
‡Packard Instrument Co., Inc.

Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Dx</th>
<th>Cr (mg %)</th>
<th>BUN (mg %)</th>
<th>Electrolytes</th>
</tr>
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<tbody>
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<td>CD</td>
<td>44</td>
<td>M</td>
<td>Nil</td>
<td>1.1</td>
<td>18</td>
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</tr>
<tr>
<td>RP</td>
<td>47</td>
<td>M</td>
<td>Nil</td>
<td>0.9</td>
<td>14</td>
<td>Nil</td>
</tr>
<tr>
<td>SH</td>
<td>52</td>
<td>M</td>
<td>Nil</td>
<td>0.8</td>
<td>15</td>
<td>Nil</td>
</tr>
<tr>
<td>MK</td>
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<td>M</td>
<td>Nil</td>
<td>0.9</td>
<td>17</td>
<td>Nil</td>
</tr>
<tr>
<td>FB</td>
<td>49</td>
<td>F</td>
<td>lone AF</td>
<td>1.2</td>
<td>24</td>
<td>Nil</td>
</tr>
<tr>
<td>FV</td>
<td>42</td>
<td>M</td>
<td>lone AF</td>
<td>0.8</td>
<td>13</td>
<td>Nil</td>
</tr>
<tr>
<td>CH</td>
<td>52</td>
<td>M</td>
<td>CAD</td>
<td>1.1</td>
<td>22</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Abbreviations: Nil = normal; lone AF = atrial fibrillation without other evidence of cardiac disease; CAD = coronary artery disease; Cr = serum creatinine concentration; BUN = blood urea nitrogen; Dx = diagnosis.

Circulation, Volume XLVII, April 1973
from an intravenous catheter in the contralateral arm, three to seven samples in the first hour and then hourly up to 10 hours. Complete urinary collection was obtained in two of these subjects from 0 to 2, 2-4, 4-6, 6-8, 8-10, and 10-24 hours after AS administration. Acetyl strophanthidin and creatinine concentrations in urine collected between 4–6 and 6–8 hours and in blood samples drawn at 5 and 7 hours after AS administration were used to calculate AS to creatinine renal clearance ratios. Creatinine concentrations were determined by alkaline picrate assay.30

Samples
Blood samples were drawn into heparinized glass tubes, centrifuged, and the plasma separated and stored at 4°C in glass vials. Urine and bile volumes were measured and aliquots stored at 4°C in glass vials. Acetyl strophanthidin concentration determinations were carried out within 2 days in the canine experiments and within 1 week in the human experiments. Values obtained were shown not to vary significantly with time over this interval.

Statistics
Statistical evaluation including least-squares linear regression analyses were performed by conventional methods.31

Results

Acetyl Strophanthidin Radioimmunoassay
Figure 1 shows a typical standard curve for plasma AS concentration, and demonstrates that the sensitivity of the assay allowed quantitation of AS concentrations as low as 0.1 ng/ml. Figure 1 also demonstrates the results of specificity studies, which showed no interference from endogenous steroid concentrations well above those occurring physiologically. False positive values were not encountered in dogs or human subjects not receiving cardiac glycosides. The precision of the method was evaluated by comparing duplicate values obtained in this study. For 135 consecutive samples run in duplicate, the mean difference between values obtained was 5.2 ± 4.9% (sd). Previous studies have documented a standard deviation of 5% or less for replicate samples determined by analogous methods.32, 33

Canine Studies
A typical semilogarithmic plot of plasma AS concentration against time following intravenous administration of 1.0 mg of AS to a 20.5-kg dog is shown in figure 2. Between 1 and 9 hours after AS infusion, the decline in plasma concentration occurred exponentially with a half-life of 79 min. Plasma concentration half-lives in the eight canine experiments ranged from 59 to 111 min with a mean value of 83 ± 19 (sd) min (table 2). The correlation coefficient for best linear fit by least-squares linear regression analysis of semilogarithmic

![Figure 1](image)

Semilogarithmic plot of duplicate determinations of percent antibody-bound 3H-ouabain in the presence of increasing concentrations of acetyl strophanthidin and of various endogenous steroids. The arrow on the vertical axis denotes binding in the absence of any competing ligand. CH = cholesterol; CO = cortisol; DHA = dehydroepiandrosterone; E = 17β-estradiol; P = progesterone; T = testosterone.

![Figure 2](image)

Semilogarithmic plot of acetyl strophanthidin plasma concentration (closed circles) and urinary excretion (open circles) vs time after a single intravenous 1.0-mg dose in a 20.5-kg dog. The half-lives of exponential decline between 1 and 9 hours were 79 min for plasma concentration and 80 min for urinary excretion.
KINETICS OF ACETYL STROPHANTHIDIN

Table 2

<table>
<thead>
<tr>
<th>Plasma Acetyl Strophanthin in Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1†</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>2†</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>3†</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>4†</td>
</tr>
<tr>
<td>Mean</td>
</tr>
</tbody>
</table>

*For best fit by least squares linear regression analysis of plot of log acetyl strophanthin concentration vs time between 60 min and 6-10 hours after intravenous doses.
†The second of two studies was carried out 4-7 days after the initial experiment.

Abbreviation: ND = not determined.

The plot of plasma AS concentration vs time ranged from 0.969 to 0.998 in the eight canine experiments (table 2). The interval between AS infusion and the onset of exponential decline of plasma AS concentration was 20, 30, 60, and 60 min in the four canine experiments in which frequent blood samples were obtained during the first hour after injection (table 2).

A semilogarithmic plot of urinary excretion of AS in the same dog is also shown in figure 2. The half-life of urinary excretion of 80 min is essentially the same as the half-life of decline in the plasma concentration. Urinary excretion half-lives ranged from 70 to 100 min in the individual canine experiments with a mean value of 79 ± 10 min (table 3). Mean total urinary excretion of AS was 133 ± 48 μg or 13.3% of the administered dose (table 3).

Table 3

<table>
<thead>
<tr>
<th>Urinary Excretion of Acetyl Strophanthin in Dogs</th>
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</thead>
<tbody>
<tr>
<td>Dog</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>1†</td>
</tr>
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<tr>
<td>2†</td>
</tr>
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<td>3†</td>
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<tr>
<td>4</td>
</tr>
<tr>
<td>4†</td>
</tr>
<tr>
<td>Mean</td>
</tr>
</tbody>
</table>

*The second of two studies in each dog was performed 4-7 days after the initial experiment.
Abbreviation: ND = not determined.

Figure 3

Semilogarithmic plot of acetyl strophanthin excretion into bile vs time after a single intravenous 1.0-mg dose in a 22-kg dog with complete biliary diversion. The half-lives of excretion were 2.3 and 2.6 hours in two experiments.
analysis of semilogarithmic plot of plasma AS concentration vs time ranged from 0.71 to 0.99 among the seven human subjects. The smaller numbers of samples obtained in two of the early studies (CD and SH) probably contributed to the lower correlation coefficients. Onset of the principal exponential phase of decline in plasma AS concentration varied from 10 to 30 min in the individual subjects with a mean of 18 ± 7 min (table 4).

A semilogarithmic plot of urinary excretion of AS in a normal male subject is also shown in figure 4. The half-life of urinary excretion of 2.5 hours is similar to the half-life of 2.3 hours for decline of the plasma AS concentration. Urinary excretion half-lives in two human subjects were 2.2 and 2.5 hours; total urinary excretion of AS in these subjects averaged 218 μg or 21.8% of the administered dose (table 5). Acetyl strophanthidin to creatinine renal clearance ratios ranged from 0.74 to 1.03 with a mean value of 0.92 ± 0.11 (SD) for four collection periods in these two subjects (table 5).

**Discussion**

The approach to measurement of subnanogram amounts of AS described here is based upon radioimmunoassay methods previously developed for digoxin, digitoxin, and ouabain. Sensitivity, precision, and specificity data for the AS assay are comparable to values obtained in those previous studies. The technic reported here also shares freedom from necessity for extraction procedures prior to measurement of AS in plasma, urine, or bile. The method is sufficiently simple and rapid to allow up to fifty duplicate determinations in a normal working day.

The pharmacokinetics of plasma AS concentration follow a pattern analogous to that previously observed for several cardiac glycosides, but with a considerably telescoped time course. The plasma level of AS after intravenous injection falls rapidly at first, presumably due to distribution from the plasma compartment into interstitial fluid and the various tissues as well as elimination. After this initial phase, the plasma level declines exponentially at a rate which appears to be determined by the rate constant for elimination of the drug.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Onset principal exponential phase (min)</th>
<th>Last sample (hr)</th>
<th>Plasma half-life (hr)*</th>
<th>Corr coeff*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>10</td>
<td>1</td>
<td>2.4</td>
<td>0.71</td>
</tr>
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<td>RP</td>
<td>25</td>
<td>14½</td>
<td>2.0</td>
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<tr>
<td>SH</td>
<td>15</td>
<td>14½</td>
<td>2.4</td>
<td>0.86</td>
</tr>
<tr>
<td>MK</td>
<td>15</td>
<td>10</td>
<td>2.3</td>
<td>0.98</td>
</tr>
<tr>
<td>FB</td>
<td>ND</td>
<td>8</td>
<td>1.9</td>
<td>0.99</td>
</tr>
<tr>
<td>FV</td>
<td>15</td>
<td>10</td>
<td>2.4</td>
<td>0.99</td>
</tr>
<tr>
<td>CH</td>
<td>30</td>
<td>8</td>
<td>2.6</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean</td>
<td>18 ± 7(SD)</td>
<td>---</td>
<td>2.3 ± 0.2(SD)</td>
<td>0.93 ± 0.10(SD)</td>
</tr>
</tbody>
</table>

*For best fit by least-squares linear regression analysis of plot of log acetyl strophanthidin vs time between 30 min and 1–8 hours after single i.v. doses.

Abbreviation: ND = not determined.
The interval of 20–60 min from intravenous injection to the onset of final exponential decline of plasma AS in dogs is considerably shorter than the previously observed intervals of 6–7 hours for ouabain\(^26\) and 5–6 hours for digoxin.\(^6,38\) Similarly, in human subjects this interval was 10–30 min for AS, 6–7 hours for ouabain,\(^37\) and 6–8 hours for digoxin.\(^39,40\)

The onset of pharmacologic effects after AS administration has also been noted to be more rapid than for the cardiac glycosides, including ouabain. For example, the time interval from intravenous injection to peak slowing of the ventricular response among patients with atrial fibrillation has been noted to be 15–20 min for AS,\(^26\) 1–2 hours for ouabain,\(^26\) and 6 hours for digoxin.\(^41\) Similarly, in an open-chest dog preparation, the time of peak increase in isometric systolic tension was earlier for AS than for ouabain, digoxin, lanatoside C, or digitoxin over a dosage range of 0.25 to 1.25 cat units.\(^2\)

After the initial rapid fall in plasma AS concentration, attributed to equilibration between the plasma and tissue compartments, the mean half-life of plasma concentration decline of 2.3 hours is about tenfold shorter than the 21.8-hour mean half-life previously observed for ouabain in man.\(^37\) Plasma concentration half-lives in man for the other commonly used cardiac glycosides are of course even longer, being about 33\(^39,40\)–51 hours\(^42\) for digoxin and 4.8 days or 115 hours for digitoxin.\(^43\) In canine experiments, the respective plasma concentration half-lives for AS, ouabain, and digoxin were 83 min, 18 hours,\(^37\) and 27 hours.\(^6\)

Prior pharmacokinetic studies have established that if at least 10% of a drug handled with first order elimination kinetics is excreted in unchanged form, a semilogarithmic plot of excreted drug vs time will generally yield a straight-line function with a half-life similar to that of plasma concentration decline.\(^36\) In the present study, 13.3 and 21.8% of administered AS was excreted in urine in canine and human experiments, respectively; and the half-life of urinary excretion of AS was similar to that for plasma concentration decline in both species. In the canine experiments, the respective mean values were 79 and 83 min; in human subjects the respective values were 2.4 and 2.3 hours. A similar relationship between urinary excretion and plasma concentration decline half-lives has been observed previously for digoxin\(^39\) and digitoxin.\(^43\)

Earlier investigations have established a similarity between half-lives of plasma concentration decline and half-times for dissipation of pharmacologic effects of ouabain and digoxin. For example, the respective plasma concentration half-lives of 21.8 hours\(^37\) and 33\(^39,40\)–51 hours\(^42\) correspond quite closely to the half-times for dissipation of positive inotropy of 22 and 33 hours as determined by serial systolic time intervals.\(^44\) Similarly, the half-times for dissipation of ventricular rate slowing in patients with atrial fibrillation of 23\(^38\) and 45 hours\(^43\) also agree well with the respective plasma concentration half-lives. Acetyl strophanthidin plasma concentration and urinary excretion half-lives noted in the present study tended to be somewhat greater than previously determined half-times for dissipation of pharmacologic effects. For example, dissipation of \((dp/dt)/P\) changes in closed-chest dogs after AS administration occurred with a half-life of 17 min,\(^5\) substantially shorter than the half-lives of AS plasma concentration decline of 83 min and urinary excretion of 79 min observed in our canine experiments. Similarly, in patients treated with AS, the half-times of dissipation of left ventricular ejection time shortening of 40 min\(^39\) and of dissipation of atrial fibrillation slowing of 80 min\(^39\) are both shorter than the plasma AS concentration and urinary excretion half-lives of 2.3 and 2.4 hours, respectively. Reflex adjustments of other determinants of myocardial contractility and of vagal tone may play a role in hastening the return toward baseline contractility and rate response to atrial fibrillation after AS administration. It is also possible that redistribution of AS from myocardium to other tissue stores, as well as elimination, may affect the time course of pharmacologic effects, a situation analogous to that described for the short-acting thiobarbiturates.\(^45\)

Urinary excretion of AS, as determined by radioimmunoassay, accounted for only 13.3 and 21.8% of the administered dose in dogs and human subjects, respectively. Biliary excretion of radioim-

---

**Table 5**

<table>
<thead>
<tr>
<th>Urinary Excretion of Acetyl Strophanthidin in Human Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>MK</td>
</tr>
<tr>
<td>FV</td>
</tr>
<tr>
<td>Mean</td>
</tr>
</tbody>
</table>

Circulation, Volume XLVII, April 1973
munoassayable AS in a dog with total biliary diversion was only 1.5–2.1% in two experiments. The remainder of the administered AS is presumed to have undergone metabolic transformation to a form or forms not detected by radioimmunoassay, or was eliminated from the body by a route other than urinary or biliary excretion. Evidence for nonbiliary gastrointestinal excretion of the cardiac glycoside ouabain has been demonstrated in dogs, and could possibly play a role in the excretion of AS as well.

In conclusion, the studies reported here indicate an apparent rate of plasma-tissue equilibration of AS, as judged by the time of onset of the final exponential phase of plasma concentration decline, which is substantially more rapid than that of previously studied cardiac glycosides, including ouabain. The rate of the final exponential decline of plasma concentration of AS is about tenfold more rapid than that of ouabain. These observations are consonant with the known brief duration of pharmacologic effects of acetyl strophanthinid.

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Circulation, Volume XLVII, April 1973
KINETICS OF ACETYL STROPHANTHIDIN


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