Single-dose daptomycin pharmacokinetics in chronic haemodialysis patients

Noha N. Salama1,2,3,4, Jonathan H. Segal2,5, Mariann D. Churchwell2,6, Jignesh H. Patel1,2, Lihong Gao7, Michael Heung2,5 and Bruce A. Mueller1,2

1University of Michigan College of Pharmacy, Department of Clinical, Social & Administrative Sciences, Ann Arbor, MI, USA, 2Renal Replacement Therapy Kinetics Study Group, Ann Arbor, MI, USA, 3Saint Louis College of Pharmacy, Division of Basic and Pharmaceutical Sciences, St. Louis, MO, USA, 4Cairo University, Faculty of Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Cairo, Egypt, 7University of Michigan School of Medicine, Department of Internal Medicine, Ann Arbor, MI, USA, 8University of Toledo College of Pharmacy, Department of Pharmacy Practice, Toledo, OH, USA and 7Cubist Pharmaceutical Inc., Lexington, MA, USA

Correspondence and offprint requests to: Bruce A. Mueller; E-mail: muellerb@umich.edu

Abstract

Background. Daptomycin has concentration-dependent antibacterial activity against Gram-positive bacteria. Its use is increasing in haemodialysis units. The manufacturer recommends a 4–6-mg/kg dose administered every 48 hrs for patients receiving haemodialysis. However, there are no published data about daptomycin pharmacokinetics and clearance during haemodialysis. The recommended dosing regimen would conflict with asymmetric thrice-weekly haemodialysis, which yields two ~44-hr and one ~68-hr interdialytic periods. This is the first study to evaluate daptomycin pharmacokinetics in haemodialysis patients, assess the extent of daptomycin dialytic removal and model serum concentrations at 44 and 68 hrs.

Methods. Six otherwise healthy subjects on chronic haemodialysis (55.3 ± 16.1 years old, three females, 66.2 ± 14.2 kg) received a single 6-mg/kg dose of daptomycin post-haemodialysis infused over 30 minutes. Serial blood samples were collected for ~44 hrs (pre-next haemodialysis) and throughout the subsequent haemodialysis session with a high permeability haemodialyser. Individual pharmacokinetic parameters determined by compartmental analysis were used to model trough serum concentrations at 44 and 68 hrs with 6-, 8- and 10-mg/kg post-haemodialysis doses.

Results. The haemodialysis session in this trial yielded mean urea and daptomycin reduction ratios of 79.6 ± 5.8% and 57.6 ± 9.2%, respectively. Daptomycin half-life was 19.4 ± 6.5 and 3.8 ± 1.1 hrs ‘off’ and ‘on haemodialysis’, respectively, with minimal rebound 1 hr post-haemodialysis. All modelled trough concentrations at 44 and 68 hrs at all doses exceed typical minimum inhibitory concentration (MIC90) values for Staphylococcus aureus and Enterococcus faecalis.

Conclusions. Daptomycin serum concentrations declined by ~50% after a 4-hr haemodialysis session with a high permeability haemodialyser. A 6-mg/kg i.v. post-haemodialysis thrice-weekly dose should result in sufficient pre-haemodialysis daptomycin serum concentrations even after a 68-hr interdialytic period.

Keywords: daptomycin; Gram-positive bacteria; haemodialysis; pharmacokinetics

Introduction

Daptomycin is a bactericidal agent with concentration-dependent activity against a broad range of Gram-positive bacteria, including methicillin- and vancomycin-resistant Staphylococcus aureus [1]. Staphylococcus aureus constitutes a substantial cause of morbidity and mortality in patients on haemodialysis [2]. Daptomycin use in haemodialysis units is likely to grow because of its spectrum of activity against Gram-positive organisms. Currently, the manufacturer’s dosing recommendations state that a 4–6-mg/kg dose every 48 hrs should be infused over 30 minutes to patients receiving haemodialysis after haemodialysis ends [1]. However, no studies have been published regarding the extent of dialytic removal of daptomycin in this population.

A typical haemodialysis schedule, Monday–Wednesday–Friday (MWF) or Tuesday–Thursday–Saturday (TTS), results in ‘uneven’ drug clearance with two ~44-hr interdialytic periods and one ~68-hr period. Within 1 week of post-haemodialysis therapy, daptomycin infusions every 48 hrs would not coincide with haemodialysis sessions and would require an additional venipuncture to adhere to the every 48 hrs dosing recommendation. With a MWF or TTS type of haemodialysis schedule, clinicians must decide whether (i) adequate serum concentrations...
can be maintained for a 68-hr interdialytic period with standard doses or (ii) higher doses need to be administered prior to the 68-hr interdialytic period, or (iii) to administer a dose at 48 hrs regardless of the haemodialysis schedule. The objectives of this investigator-initiated study were to evaluate daptomycin pharmacokinetics, quantify daptomycin dialytic removal and model its disposition in a 44- and 68-hr interdialytic period in end-stage renal disease (ESRD) patients on thrice-weekly chronic haemodialysis schedules.

Subjects and methods

Study design

This study was part of a non-blinded prospective clinical trial in otherwise healthy adults with ESRD conducted at the University of Michigan in 2007–08, which addressed multiple distinct objectives. Patients receiving chronic thrice-weekly outpatient haemodialysis at the University of Michigan outpatient haemodialysis clinics were recruited. One part of the study addressed the feasibility of intradialytic daptomycin infusion as an administration strategy for dosing daptomycin in ESRD patients on haemodialysis using haemodiafilters of different permeabilities. Those findings have been recently published [3]. The second part of this trial, described herein, aimed to quantify the extent of daptomycin dialytic removal and to assess and model daptomycin disposition following a single manufacturer-recommended 6-mg/kg post-haemodialysis dose. Because daptomycin removal by haemodialysis has not been published previously, we aimed to obtain baseline pharmacokinetic information in this patient population and to serve as a basis for a larger pharmacokinetic trial. Six subjects were considered to be sufficient for this pilot study.

Patients were considered for inclusion into the study if they were ≥18 years of age, had ESRD and received chronic maintenance haemodialysis for at least 6 months, were within 40% of ideal body weight and >40 kg, had no acute concurrent illness or evidence of infection and were compliant with their thrice-weekly maintenance haemodialysis schedule. Medical records were reviewed to ensure subjects had not received daptomycin within the month prior to enrollment in the study. The exclusion criteria were: pre-study haemoglobin <11 g/dL, plasma albumin <2.5 g/dL, unstable blood pressure control, need for routine large fluid removal during haemodialysis (>4 L) and creatine phosphokinase (CPK) >600 U/L or >3 times the upper limit of normal. Subjects who were already enrolled in other investigational drug studies, allergic to daptomycin, or had significant liver disease (subjects with Child-Pugh class C), HIV, or who experienced any signs and symptoms of myopathy (muscle pain or weakness) were also excluded from the study. The study protocol was approved by the University of Michigan Institutional Review Board (IRB). The study was conducted at the University of Michigan outpatient haemodialysis Unit and General Clinical Research Center (GCRC).

Subjects identified by investigators who met the inclusion/exclusion criteria were invited to participate, and informed consent was obtained. At baseline, all subjects underwent a routine physical exam, and all pertinent labs as described in the inclusion/exclusion criteria were assessed. The initial patient interview documented the study subject’s medical, drug therapy, history of allergy(a), and included age, gender, weight, and race.

Subjects received their usual haemodialysis session using their usual haemodialysers (polysulphone, F-200NR, surface area 2.0 m², ultrafiltration coefficient 62 ml/h/mmHg, Fresenius Medical Care, Walther, MA) in the hospital haemodialysis unit. Once haemodialysis ended, subjects were transported to the GCRC, where they received a 6-mg/kg (based on post-haemodialysis weight) daptomycin dose infused intravenously (i.v.) over 30 minutes. Serial blood samples were obtained pre-infusion, at the end of the infusion and at 1, 2, 3, 4, 24 and 44 hrs (time next haemodialysis session started) from the start of the infusion to determine the pharmacokinetics of daptomycin ‘off haemodialysis.’ The 44-hr blood sample was obtained at the haemodialysis unit immediately prior to the initiation of the next haemodialysis session from the needle that was already placed for the impending haemodialysis session. Additional ‘on-haemodialysis’ blood samples were obtained midway and at the end of this second haemodialysis session. A final serum concentration was obtained 1 hr post-haemodialysis to determine whether any daptomycin rebound occurred at this time point. The second haemodialysis session was fixed to conclude after 4 hrs of haemodialysis. The haemodialysis sessions used patients’ usual blood (average 400 mL/min) and dialysate flow rates (average 700 mL/min). Blood urea nitrogen was measured pre- and immediately post-haemodialysis to assess urea reduction ratio. Daptomycin doses were prepared by the University of Michigan Investigational Drug Service on the day of the study in accordance with the manufacturer’s recommendations.

Liquid chromatography/mass spectrometry (LC/MS/MS) assay methodology

Serum was separated by centrifugation, and the daptomycin concentrations were analysed by a LC/MS/MS method reported earlier by our research group [3]. Briefly, human serum (Bioreclamation Inc., Liverpool, NY) was used as a matrix blank to build the calibration standard curve (1.0 to 100 µg/mL) using a daptomycin analogue, CB-183253, as internal standard. The analytical reference standard daptomycin, along with the internal standard, were provided by Cubist Pharmaceuticals Inc. The instrumentation included an Agilent Bioanalyzer API-3000 coupled with an Agilent 1100 Quaternary Pump and a Leap CTC Auto-sampler. A 5% 3-(3-cholamidopropyl) dimethylammonio]1-propane sulfonate (CHAPS) solution (50 mM in 0.1% formic acid) was added to calibration standards, quality control samples and study samples. The 50-µL serum samples were mixed with 400 µL internal standard, CB-183253, 5.0 µg/mL in 0.1% trifluoroacetic acid in acetonitrile solution. The mixture was vortexed for 10 minutes and then centrifuged (3000 rpm, 10 minutes, 4°C). The 250-µL supernatant was dried under nitrogen gas and reconstituted with 100 µL 5 mM CHAPS in 0.1% formic acid water solution and analysed by LC/MS/MS. Multiple ions reactions monitor (MRM) transitions on mass spectrometer of 811 to 159 and 837 to 365 were used to monitor daptomycin and internal standards, respectively.

The LC/MS/MS assay lowest limit of quantification (LLOQ) was 1.0 µg/mL. The specificity of the assay was performed by analysing six individual lots of blank matrix. There were no interference peaks observed. The sample analysis was completed in five analytical batches. The coefficient of variation (%CV) for the calibration standard varied from 6.9% to 11.8%, and the percent relative residual error (% RRR) varied from −2.7% to 7.2%. The %CV for the batch quality control standards varied from 10.0% to 11.6%, and %RRR varied from −5.0% to 3.9%. Overall analytical results were acceptable, and sample analysis results were reported.

Data analysis

Daptomycin pharmacokinetics was assessed ‘off’ and ‘on haemodialysis’. Pharmacokinetic compartmental analysis was performed applying different weighting schemes using WinNonlin software, version 5.2.1 (Pharsight Corporation, Mountain View, CA) for the ‘off haemodialysis’ samples from 0 to ~44 hrs. Selection of the pharmacokinetic model was based on the goodness of fit criteria (visual inspection, final residual sum of squares, weighted residual sum of squares, random distribution of residuals, Akaike information criteria and Schwartz criteria). Both one- and two-compartment analyses were evaluated to determine the best model fit. Various weighting schemes included a weight of 1, 1/Y (where Y is the drug concentration), 1/Y², 1/predicted concentration (iterative re-weighting) and 1/predicted concentration squared. The individual pharmacokinetic parameters determined by compartmental analysis subsequently were used to simulate daptomycin serum concentrations at 44 and 68 hrs at 6-, 8- and 10-mg/kg doses.

Daptomycin elimination constant ‘on-haemodialysis’ was calculated from the slope of the serum concentration time curve using the data collected immediately prior to, midway and at the end of the subsequent haemodialysis session consistent with the methodology used with other drugs.
The reduction ratios for urea and daptomycin were calculated as follows:

Percent reduction ratio = \frac{\text{Preh} - \text{haemodialysis serum concentration} - \text{Posth} - \text{haemodialysis serum concentration}}{\text{Preh} - \text{haemodialysis serum concentration}} \times 100

Results

Six otherwise healthy ESRD patients on chronic haemodialysis (age 55.3 ± 16.1 years old, three females, 66.2 ± 14.2 kg, body mass index 22.5 ± 3.3 kg/m², three African-Americans, two Caucasians and one Native American) were enrolled and completed this pilot study. No women of child bearing age were enrolled in this study. Study subjects continued all their usual maintenance medications while on this study. All subjects scored below the minimum Child_pugh class A score and had serum albumin concentrations >3.8 g/dL. The causes of underlying renal failure were diabetes (two subjects), hypertension (one subject) and glomerulonephritis (three subjects). The length of time the subjects received chronic on haemodialysis prior to the study ranged from 8 to 331 months. None of the enrolled subjects had residual renal function. Subjects received their haemodialysis via arteriovenous fistula (three subjects), arteriovenous graft (two subjects) and tunneled catheter (one subject). The average ultrafiltration volume during the haemodialysis treatment was 2.8 ± 1.4 L. During the study, none of the subjects experienced chronic hyperkalaemia or any other adverse effects attributable to daptomycin.

All enrolled subjects received a single 6-mg/kg dose of daptomycin as a 30-minute i.v. infusion after haemodialysis. Eleven samples were collected from each subject over a 49-hr period. A two-compartment i.v. infusion model (1/predicted concentration squared-weighting scheme) with first order elimination appeared to provide an improved fit of daptomycin serum concentrations for each subject compared to the one compartment model based on the goodness of fit criteria. All daptomycin serum concentrations prior to infusion were below the LLOQ. The observed daptomycin maximum serum concentration (Cmax, mean ± SD) was 61.1 ± 7.6 (range: 52.2–69.6) µg/mL. The mean ± SD for the observed daptomycin serum concentrations are displayed in Figure 1. Daptomycin half-life (T1/2) 'off-haemodialysis' was 19.4 ± 6.5 hrs, with Subject 2 showing notably faster drug elimination. Subjects received their regularly scheduled haemodialysis session at ~44 hrs following daptomycin infusion. The average urea reduction ratio for these patients was 79.6 ± 5.8%. Daptomycin serum concentrations measured immediately prior, midway and at the end of this weekly haemodialysis session were 15.4 ± 2.7, 10.3 ± 1.7 and 6.4 ± 1.4 µg/mL, respectively. Daptomycin elimination rate constant 'on haemodialysis' was calculated to be 0.20 ± 0.05 hr⁻¹, and T1/2 was 3.77 ± 1.12 hrs. The average serum concentration measured 1 hr post-haemodialysis was 7.3 ± 0.8 µg/mL, indicating limited drug rebound at 1 hour. Daptomycin reduction ratio was 57.6 ± 11% when we used the serum concentrations at the end of a 4-hr haemodialysis session and was 51.7 ± 9.2% when we used the 1-hr post-haemodialysis serum concentrations.

The individual pharmacokinetic parameters (Table 1) determined by compartmental analysis were used to simulate the serum concentrations at 44 and 68 hrs at 6-, 8- and 10-mg/kg doses (Table 2). For example, serum concentrations at 44 hrs represent the pre-haemodialysis residual concentration on Wednesday following an initial Monday
post-haemodialysis dose. Similarly, the 68-hr serum concentration represents the drug residual serum concentration on Monday morning following a Friday post-haemodialysis daptomycin dose. In these simulations, all subjects would have maintained serum concentrations >4 μg/mL, which is above the concentrations at which S. aureus (≤1 μg/mL) and Enterococcus faecalis (≤4 μg/mL) isolates are considered daptomycin susceptible [1], throughout a 68-hr interdialytic period.

### Discussion

This is the first study to address daptomycin pharmacokinetics and characterize the extent of its dialytic removal following a single 6-mg/kg post-haemodialysis dose in ESRD patients. Daptomycin pharmacodynamics in haemodialysis patients has also been investigated recently. Sader et al. compared S. aureus antimicrobial susceptibility patterns in haemodialysis patients and found that they were similar to those reported in other patient populations [6]. In those studies, the authors re-confirmed the high potency of daptomycin against S. aureus strains [minimum inhibitory concentration (MIC<50)/MIC<90 = 0.25/0.5 μg/mL] in haemodialysis patients. Daptomycin antimicrobial activity is concentration-dependent. The Cmax/MIC and area under the serum concentration time curve (AUC)/MIC ratios are the pharmacokinetic–pharmacodynamic indices most predictive of clinical efficacy [7–11]. Consequently, increase in these ratios optimizes daptomycin efficacy. Pharmacokinetic–pharmacodynamic target attainment analysis using Monte Carlo simulation evaluated daptomycin 4- and 6-mg/kg dosing regimens in the context of clinically relevant MIC values (0.25–1 μg/mL). The AUC/MIC targets for daptomycin antibacterial activity were reported to be <1 for a 6-mg/kg dose, suggesting potent antimicrobial activity (Ambrose PG et al., 48th International Conference on Antimicrobial Agents and Chemotherapy/46th Annual Meeting of the Infectious Diseases Society of America, 2008).

Because the antimicrobial efficacy of daptomycin is dependent on the Cmax achieved [12,13], high peak concentrations are desirable. However, higher peaks are also associated with higher troughs, and prolonged high trough concentrations (≥25 mg/L) have been linked with CPK elevations in patients with bacteraemia and/or endocarditis (Bhavnani SM et al., 46th International Conference on Antimicrobial Agents and Chemotherapy, 2006). Therefore, knowledge of daptomycin pharmacokinetics is imperative in order for the clinician to properly balance efficacy with potential risks.

The urea reduction ratio achieved by the haemodialysis session in this trial was ~80% which is equivalent to an estimated kt/V of ~1.6 [14], suggesting an adequate haemodialysis session was delivered to these subjects. Sica et al. measured dialysate daptomycin concentrations and reported 15% of a 4-mg/kg administered dose was lost

### Table 1. Pharmacokinetic parameters for six ESRD patients following 30-minute i.v. infusion of a single 6-mg/kg daptomycin dosing in the absence of haemodialysis

<table>
<thead>
<tr>
<th></th>
<th>Volume of distribution (L/kg)</th>
<th>Half-life (hrs)</th>
<th>Clearance (mL/min)</th>
<th>Modelled Cmax (μg/mL)</th>
<th>Observed Cmax (μg/mL)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (μg × hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td>0.11</td>
<td>26.9</td>
<td>3.1</td>
<td>52.0</td>
<td>52.2</td>
<td>2177</td>
</tr>
<tr>
<td>Subject 2</td>
<td>0.04</td>
<td>8.6</td>
<td>4.8</td>
<td>69.0</td>
<td>68.8</td>
<td>1836</td>
</tr>
<tr>
<td>Subject 3</td>
<td>0.08</td>
<td>20.1</td>
<td>3.5</td>
<td>59.3</td>
<td>56.0</td>
<td>2164</td>
</tr>
<tr>
<td>Subject 4</td>
<td>0.08</td>
<td>19.3</td>
<td>2.7</td>
<td>65.7</td>
<td>69.6</td>
<td>2103</td>
</tr>
<tr>
<td>Subject 5</td>
<td>0.11</td>
<td>16.4</td>
<td>4.7</td>
<td>51.8</td>
<td>55.1</td>
<td>1326</td>
</tr>
<tr>
<td>Subject 6</td>
<td>0.06</td>
<td>24.8</td>
<td>1.4</td>
<td>63.4</td>
<td>64.8</td>
<td>3404</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.08 ± 0.03</td>
<td>19.4 ± 6.5</td>
<td>3.4 ± 1.3</td>
<td>60.2 ± 7.1</td>
<td>61.1 ± 7.6</td>
<td>2168 ± 686</td>
</tr>
</tbody>
</table>

Cmax = maximum serum concentration, AUC<sub>0-∞</sub> = area under the serum concentration time curve assuming no haemodialysis.

### Table 2. Simulated daptomycin serum concentrations and area under the curves following 30-minute i.v. infusion of a single dose of 6, 8 and 10 mg/kg administered after haemodialysis to six subjects with ESRD

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Simulated doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 mg/kg</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>60.2 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>(52.0–69.0)</td>
</tr>
<tr>
<td>Concentration at 44 hrs (μg/mL)</td>
<td>15.8 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>(10.8–19.6)</td>
</tr>
<tr>
<td>Concentration at 68 hrs (μg/mL)</td>
<td>10.9 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>(6.2–16.1)</td>
</tr>
<tr>
<td>AUC (0–68 hrs) (μg × hr/mL)</td>
<td>1351 ± 154</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD (range). Daptomycin-simulated serum concentrations at 44 hrs, 68 hrs and the AUC (0–68 hrs) were determined assuming no haemodialysis occurs following daptomycin administration.
in a 4-hr haemodialysis session (Sica et al., 42nd International Conference on Antimicrobial Agents and Chemo-therapy, 2002). However, the decline in daptomycin serum concentrations from that haemodialysis session was not reported. The decline in daptomycin serum concentration with haemodialysis in our study is interesting because the molecular weight of daptomycin is large (1621 Daltons), and the percent plasma protein binding is approximately 90% [3, 15–17]. However, a factor that mainly contributes to increased daptomycin dialysability is the observed small volume of distribution (0.08 ± 0.03 L/kg), similar to that observed in healthy volunteers (~0.1 L/kg [15–17]). We used a highly permeable haemodialysis membrane. These high permeability haemodialysers are being used increasingly in clinical practice, and membrane permeability likely affects daptomycin haemodialysis clearance [3].

In a population pharmacokinetic study pooling results from many trials, Dvorchik et al. calculated a median ‘off haemodialysis’ half-life of 29.3 hrs (range: 14.7–41.8 hrs) and a median volume of distribution of 6.6 L (range: 3.8–13.2 L) [18]. These findings are comparable to ours (median half-life of 19.7 hrs (range: 16.4–26.9 hrs) and volume of distribution of 5.2 L (range: 3.0–7.2 L). The half-life observed by Dvorchik et al. and that observed in our study are 2–3-fold longer than that seen in individuals with normal renal function [15–17]. This was the basis for our hypothesis that a 3-day interdialytic period may indeed result in the maintenance of therapeutic daptomycin serum concentrations despite the manufacturer’s every 48 hrs dosing recommendation. In our pharmacokinetic simulations, all subjects would have maintained serum concentrations that exceed daptomycin MIC90 for S. aureus and E. faecalis isolates at 68 hrs. Therefore, based on our modelling, daptomycin concentrations can be expected to remain effective on Monday morning following Friday post-haemodialysis dosing (equivalent to a 68-hr interdialytic period). Importantly, these pharmacokinetic data were determined from a single dose. Consequently, there will be some residual daptomycin post-haemodialysis, and subsequent doses will yield even higher pre- and post-haemodialysis serum concentrations. The potential risk of adverse effects from multiple dosing of conventional doses warrants further investigation.

This study has some limitations. We obtained data from a limited sample size of six patients and were limited to 11 blood samples per patient per our IRB approval of this single-dose pilot study because of patient safety concerns in this anaemic population. However, most of our samples were timed to appropriately characterize the pharmacokinetic profile of the drug “off haemodialysis”. Additionally, we did not collect the dialysate in our study because assay sensitivity limitations precluded the ability to accurately measure the low daptomycin dialysate concentrations.

Based on our modelling, we conclude that it seems likely that adequate daptomycin serum concentrations are maintained in a 2- and 3-day interdialytic period when a 6-mg/kg post-haemodialysis dose is used. Moreover, it appears that higher daptomycin doses are not necessary to account for the 68-hr interdialytic period for patients receiving chronic asymmetric thrice-weekly haemodialysis treatments despite the manufacturer’s 48 hrs dosing recommendation. The findings of this pilot study should serve as guidance for a prospective clinical trial with larger patient enrollment. Multiple-dose pharmacokinetics of daptomycin in haemodialysis patients should be validated prospectively.

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Conflict of interest statement. B.A.M. serves on the speaker’s bureau for Cubist.

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