Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism

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Background. Endothelin is a potent vasoconstrictor that has been implicated in the pathogenesis of radiocontrast nephrotoxicity. Endothelin antagonists may reduce the renal hemodynamic abnormalities following radiocontrast administration.

Methods. One hundred fifty-eight patients with chronic renal insufficiency [mean serum creatinine ± SD = 2.7 ± 1.0 mg/dL (242.3 to ± 92.8 μmol/L)] and undergoing cardiac angiography were randomized to receive either a mixed endothelin A and B receptor antagonist, SB 290670, or placebo. All patients received intravenous hydration with 0.45% saline before and after radiocontrast administration. Serum creatinine concentrations were measured at baseline, 24 hours, 48 hours, and 3 to 5 days after radiocontrast administration. The primary end point was the mean change in serum creatinine concentration from baseline at 48 hours; the secondary end point was the incidence of radiocontrast nephrotoxicity, defined as an increase in serum creatinine of ≥0.5 mg/dL (44 μmol/L) or ≥25% from baseline within 48 hours of radiocontrast administration.

Results. The mean increase in serum creatinine 48 hours after angiography was higher in the SB 209670 group (0.7 ± 0.7 mg/dL (63.5 ± 58.6 μmol/L)) than in the placebo group (0.4 ± 0.6 mg/dL (33.6 ± 55.1 μmol/L), P = 0.002). The incidence of radiocontrast nephrotoxicity was also higher in the SB 209670 group (56%) compared with placebo (29%, P = 0.002). This negative effect of SB 209670 was apparent in both diabetic and nondiabetic patients. Adverse effects, especially hypotension or decreased blood pressure, were more common in the SB 209670 group.

Conclusions. In patients with chronic renal insufficiency who were undergoing cardiac angiography, endothelin receptor antagonism with SB 209670 and intravenous hydration exacerbate radiocontrast nephrotoxicity compared with hydration alone.

Radiocontrast nephrotoxicity is a common and important cause of hospital-acquired renal insufficiency [1-4]. Although the pathogenesis of radiocontrast nephrotoxicity is not clearly defined, an imbalance between vasodilatory and vasoconstrictive factors has been proposed as a mechanism for causing renal medullary ischemia [5].

Endothelin is an endogenous peptide with potent vasoconstrictor effects, including preferential reduction of intrarenal blood flow [6, 7]. In animals, significant increases in both plasma and urinary endothelin levels have been observed during and after intravenous radiocontrast administration [8]. Furthermore, endothelin receptor antagonists have been found to prevent renal vasoconstriction in animal models of radiocontrast nephrotoxicity [9, 10]. However, to our knowledge, there have been no studies of these antagonists for the prevention of radiocontrast nephrotoxicity in humans.

SB 209670 [(1RS-2SR, 3RS)-3-(2-carboxymethoxy-4-methoxy-phenyl)-5-(prop-1-xyloxy)indane-2-carboxylic acid; SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA] is a novel, nonpeptide-mixed endothelin receptor A and B (ET_A and ET_B) antagonist. In animals, infusion of SB 209670 prior to radiocontrast administration resulted in a significant increase in renal blood flow and attenuated the reduction in glomerular filtration rate [10]. This multicenter, prospective, randomized study was performed to determine whether or not the administration of SB 209670 prevents increases in serum creatinine concentration and reduces the incidence of radiocontrast nephrotoxicity in a group of patients at high risk for this complication while undergoing cardiac angiography.

METHODS

Study population

A total of 158 patients was randomized between November 1996 and November 1997 at 23 hospitals in the United States. Adult patients undergoing cardiac angiog-
raphy with serum creatinine ≥2.0 mg/dL (176.8 μmol/L) within 48 hours prior to radiocontrast administration were eligible for the study. Exclusion criteria were a supine blood pressure of <100/70 mm Hg or a heart rate of >100 beats per minute at baseline, acute renal failure, chronic renal failure requiring dialysis, inability to adhere to the hydration regimen, diuretic therapy within 12 hours or during infusion of study drug, dopamine therapy within six hours or during infusion of study drug, administration of nonsteroidal anti-inflammatory drugs other than aspirin (≤325 mg per day) within 24 hours of study drug, uncontrolled cardiac arrhythmia, hepatic dysfunction, cerebrovascular accident within one week, and women of child-bearing potential. All patients received ≥50 ml of intra-arterial low osmolar radiocontrast. The indications for angiography and the choice of low osmolar radiocontrast were determined by each patient’s cardiologist and were based on clinical needs. The protocol was approved by the institutional review board at each institution, and all patients gave written informed consent.

**Study protocol**

The study design involved a double-blind random assignment of patients to receive either SB 209670 (100 μg/kg of ideal body weight over 10 min, followed by an infusion of 1.0 μg/kg per min) or placebo. This dose of SB 209670 was found to result in a steady-state plasma SB 209670 concentration of approximately 1200 ng/mL. In prior studies, this dose was the highest tolerated dose in older or hypertensive patients and resulted in a modest reduction in blood pressure in patients with essential hypertension (abstract; *Am J Hypertens* 11:171A, 1998). All patients received 0.45% saline intravenously at a rate of 1 mL/kg of body weight per hour beginning 2 to 12 hours prior to and continuing for at least 12 hours after radiocontrast administration.

SB 209679 or placebo was begun 30 to 150 minutes before radiocontrast administration and was infused for 12 hours; interventions for coronary artery disease were postponed for 48 hours after radiocontrast administration unless necessitated by refractory ischemia. Infusion of the study drug was terminated early for the development of heart rate >130 beats per minute, hypotension not responsive to intravenous fluids (systolic blood pressure <80 mm Hg or a decrease in systolic or diastolic blood pressure >30 mm Hg), symptoms or signs of organ hypoperfusion, need for protocol-prohibited medications, or any other severe adverse effect. Vital signs were measured at baseline, prior to initiation of study medication, every 10 minutes for the first hour, every hour for the next 11 hours, and then every 4 hours for 12 hours. Serum creatinine measurements were performed at baseline and at 24 hours, 48 hours, and 3 to 5 days after the initiation of study medication.

**Study end points**

The primary end point of the study was the mean change in serum creatinine from baseline value at 48 hours after radiocontrast administration. The predefined secondary end points were the incidence of radiocontrast nephrotoxicity, peak serum creatinine level, and duration of hospitalization. Radiocontrast nephrotoxicity was defined as a ≥0.5 mg/dL (44 μmol/L) or ≥25% increase in serum creatinine concentration from baseline within 48 hours of radiocontrast administration.

**Statistical analysis**

Randomization was performed locally by means of sealed envelopes. A hospital pharmacist was designated as the unblinded third party for preparation of the study drugs and random assignment of treatment.

A sample size of 172 patients (86 per treatment group) was initially planned in order to detect a 0.5 mg/dL (44 μmol/L) difference in serum creatinine between SB 209670 and placebo, assuming a standard deviation of change in serum creatinine from baseline of 0.8 mg/dL (71 μmol/L) for both treatment groups, with 90% power and a two-tailed significance level of 0.05.

Data are reported as mean values ± SD for continuous variables and as percentages for discrete variables. Continuous variables were analyzed by two-tailed t-test and discrete variables by the chi-square test or Fisher’s exact test. A *P* value of less than 0.05 was considered statistically significant. The percentage of patients with an increase in serum creatinine of 0.5 mg/dL (44 μmol/L) or ≥25% increase over baseline after radiocontrast administration was evaluated by Cochran-Mantel-Haenszel methodology with center as strata. The change in serum creatinine concentration and peak serum creatinine concentration was analyzed by a general linear model.

The serum creatinine level at 48 hours after radiocontrast administration, the change in serum creatinine at 48 hours from baseline value, and the incidence of nephrotoxicity for each treatment group were compared separately for diabetic versus nondiabetic patients. Standard *t*-test analyses were used in comparing the creatinine values. Logistic regression was used for the comparison of nephrotoxicity.

In order to assess the effects of treatment with SB 209670 and diabetes, four models were created for each end point. One model used the presence or absence of diabetes as the predictor, while another model used the treatment group as the predictor in order to evaluate the univariable effects of these factors on the end points. The third model assessed both diabetes and treatment group for any independent effect. The final model included diabetes, treatment group and the interaction of diabetes and treatment to test for a differential treatment effect in diabetic versus nondiabetic patients. General
linear modeling techniques were used for the continuous creatinine value end points. Logistic regression modeling techniques were used for nephrotoxicity. All analyses were performed with SAS version 6.08 (SAS Institute, Cary, NC, USA).

**RESULTS**

One hundred fifty-eight patients were randomized in this study. At 48 hours after cardiac angiography, 132 out of 158 patients had serum creatinine measurements available for the analysis of efficacy.

Table 1 shows the baseline characteristics of the two study groups; no significant differences were detected between the groups. The number of patients with diabetes mellitus or congestive heart failure was similar in both groups, as was the number receiving calcium-channel antagonists before angiography. The volume of radiocontrast agent given in the two groups was also similar.

Baseline serum creatinine concentrations were similar for the two treatment groups \((P = 0.842)\). At 48 hours after radiocontrast administration, there was a trend toward a higher mean serum creatinine concentration in the SB 209670 group compared with the placebo group \([3.5 \pm 1.2 \text{ mg/dL} \ (308.9 \pm 104.9 \ \mu\text{mol/L}) \text{ vs. } 3.1 \pm 1.2 \text{ mg/dL} \ (277.1 \pm 105.2 \ \mu\text{mol/L}), \text{ respectively, } P = 0.062]\).

At three to five days follow-up after cardiac angiography, there was no significant difference in the mean serum creatinine concentration between patients treated with SB 209670 and those who received placebo \([3.6 \text{ mg/dL} \ (315.4 \ \mu\text{mol/L}) \text{ vs. } 3.4 \text{ mg/dL} \ (301.5 \ \mu\text{mol/L}), \text{ respectively, } P = 0.880]\). The mean time to peak serum creatinine concentration was 57.1 hours in the SB 209670 group and 56.2 hours in the placebo group \((P = 0.910)\).

For the primary end point, the increase in serum creatinine concentration was significantly greater at both 24 and 48 hours in the SB 209670 group than in the placebo group (Table 2). At 24 hours, the mean increase in serum creatinine concentration was \(0.3 \pm 0.4 \text{ mg/dL} \ (30.0 \pm 32.1 \ \mu\text{mol/L})\) for the SB 209670 group compared with \(0.1 \pm 0.3 \text{ mg/dL} \ (9.6 \pm 25.8 \ \mu\text{mol/L})\) for the placebo group \((P = 0.00003)\); at 48 hours, the mean increase in serum creatinine concentration was \(0.7 \pm 0.7 \text{ mg/dL} \ (63.5 \pm 58.6 \ \mu\text{mol/L})\) compared with \(0.4 \pm 0.6 \text{ mg/dL} \ (33.6 \pm 55.1 \ \mu\text{mol/L}), \text{ respectively, } P = 0.002\).

At 48 hours after cardiac angiography, the incidence of radiocontrast nephrotoxicity was significantly higher in patients who received SB 209670 compared with those who received placebo \((56 \text{ vs. } 29\%, \ P = 0.002)\), reflecting a relative risk of \(1.82 \ (95\% \ CI, 1.19 \text{ to } 2.77)\). There was no difference in duration of hospitalization between SB 209670 and placebo groups \((10.8 \pm 8.8 \text{ vs. } 10.3 \pm 8.2 \text{ days}, \ P = 0.430)\).

Of the total study population, 100 out of 158 patients had diabetes mellitus; of the patients included in the analysis of efficacy, 84 out of 132 had diabetes mellitus. Baseline serum creatinine levels were similar for diabetic versus nondiabetic patients \([2.9 \pm 1.0 \text{ mg/dL} \ (252.6 \pm 90.1 \ \mu\text{mol/L}) \text{ vs. } 2.6 \pm 1.0 \text{ mg/dL} \ (227.3 \pm 85.2 \ \mu\text{mol/L}), \text{ respectively, } P = 0.131]\). Radiocontrast nephrotoxicity occurred in 45 out of 84 \((54\%)\) patients with diabetes mellitus, and in 11 out of 48 \((23\%)\) nondiabetic patients \((P < 0.001)\). Among patients with diabetes, the mean increase in serum creatinine concentration and the incidence of radiocontrast nephrotoxicity were significantly greater for the SB 209670 group compared with placebo (Table 2). Furthermore, diabetic patients who received SB 209670 had an absolute increase in serum creatinine and an incidence of radiocontrast nephrotoxicity that was significantly higher than nondiabetics who received SB 209670.

When the relative increases in serum creatinine were evaluated with respect to diabetic status, SB 209670 resulted in a 45\% increase among diabetic patients compared with a 43\% increase among nondiabetic patients. Logistic regression modeling of the interaction between treatment and diabetes on the end point of radiocontrast nephrotoxicity demonstrated that the effect of SB 209670 on the incidence of radiocontrast nephrotoxicity was not statistically different in diabetic versus nondiabetic patients \((P = 0.356)\).

Adverse effects were more frequent in the SB 209670 treatment group compared with placebo (Table 4). In the SB 209670 group, nine \((12\%)\) patients were withdrawn from the study during the 48-hour period after radiocontrast administration because of adverse events compared with three \((4\%)\) patients in the placebo group. In the SB 209670 treatment group, decreased blood pressure \((\text{either a transient decrease or hypotension as defined earlier in this article})\) occurred in 14 \((18\%)\) patients; in the placebo group, these adverse effects occurred in eight \((10\%)\). Among the 14 out of 77 patients in the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SB 209670 ((N = 77))</th>
<th>Placebo ((N = 81))</th>
</tr>
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<tbody>
<tr>
<td>Age years</td>
<td>64.6 ± 12.1</td>
<td>66.6 ± 10.1</td>
</tr>
<tr>
<td>Sex male/female</td>
<td>51/26</td>
<td>59/22</td>
</tr>
<tr>
<td>Weight kg</td>
<td>84.7 ± 18.4</td>
<td>84.3 ± 19.6</td>
</tr>
<tr>
<td>Systolic mm Hg</td>
<td>148 ± 26</td>
<td>148 ± 26</td>
</tr>
<tr>
<td>Diastolic mm Hg</td>
<td>79 ± 14</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>Serum creatinine mg/dL</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>53 (69)</td>
<td>47 (58)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>37 (48)</td>
<td>44 (54)</td>
</tr>
<tr>
<td>Calcium-channel antagonist therapy</td>
<td>36 (44)</td>
<td>39 (48)</td>
</tr>
<tr>
<td>Volume of radiocontrast agent mL</td>
<td>104.0 ± 64.8</td>
<td>122.4 ± 86.2</td>
</tr>
<tr>
<td>Duration of IV hydration hours</td>
<td>21.7 ± 10.9</td>
<td>24.1 ± 14.8</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

*Table 1. Baseline characteristics of the two treatment groups*
Table 2. Change in serum creatinine for the treatment groups

<table>
<thead>
<tr>
<th></th>
<th>SB 209670</th>
<th>Placebo</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.7±0.9</td>
<td>2.8±1.2</td>
<td>—</td>
</tr>
<tr>
<td>24 hours</td>
<td>3.1±1.1</td>
<td>3.1±1.2</td>
<td>0.3±0.7 (±12.9%)</td>
</tr>
<tr>
<td>48 hours</td>
<td>3.5±1.2</td>
<td>3.1±1.2</td>
<td>0.7±0.7 (±27.8%)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. SCr is serum creatinine concentration.

<sup>a</sup>P value for the comparison of mean change from baseline between the two groups.

Table 3. Serum creatinine concentration at baseline and 48 h after radiocontrast administration according to treatment group and presence or absence of diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>Diabetes present (N = 84)</th>
<th>Diabetes absent (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SB 209670</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(N = 45)</td>
<td>(N = 39)</td>
</tr>
<tr>
<td>Baseline serum creatinine mg/dL</td>
<td>2.9±1.0</td>
<td>2.9±1.0</td>
</tr>
<tr>
<td>Serum creatinine 48 h after radiocontrast administration mg/dL</td>
<td>3.7±1.2</td>
<td>3.3±1.3</td>
</tr>
<tr>
<td>Increase in serum creatinine at 48 h mg/dL</td>
<td>0.9±0.7</td>
<td>0.5±0.7</td>
</tr>
<tr>
<td>Incidence of radiocontrast nephrotoxicity %</td>
<td>30/45 (67%)</td>
<td>15/39 (39%)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

SB 209670 treatment group who developed either frank hypotension or decreased blood pressure, the mean increase in serum creatinine concentration at 48 hours after radiocontrast administration was 0.5 ± 0.5 mg/dL (42.8 ± 42.1 μmol/L), compared with 0.8 ± 0.7 mg/dL (73.1 ± 60.7 μmol/L) in 63 out of 77 patients who did not experience this complication (P = 0.080).

DISCUSSION

Radiocontrast nephrotoxicity is a common cause of hospital-acquired renal failure and is a well-recognized complication of cardiac angiography. Depending on the definition of radiocontrast nephrotoxicity and the patient population, the incidence has been reported to occur in 0 to 58% of patients after radiocontrast administration [11–14]. Furthermore, patients who develop radiocontrast nephrotoxicity have a significantly higher mortality rate compared with patients who do not develop this complication, even after adjustment for differences in comorbidity [4]. A number of therapies, particularly the use of intravenous hydration [15], diuretic agents [15], and nonionic radiocontrast media [16, 17], have been evaluated for reducing the risk of this complication. In this study, we evaluated a novel endothelin receptor antagonist in patients at high risk for developing radiocontrast nephrotoxicity after cardiac angiography.

Endothelins, a peptide family of closely related isoforms, act on two distinct subtypes of receptors called ET<sub>A</sub> and ET<sub>B</sub> receptors [18, 19]. In the past, ET<sub>A</sub> receptors were believed to mediate the vasoconstrictor effects of endothelins, whereas ET<sub>B</sub> receptors were thought to produce vasodilatory effects. However, both subtypes of receptors have recently been found to be involved in the vasoconstrictor action of endothelins in human blood vessels [20]. The relative contribution of each subtype to the vasopressor effects of endothelins is believed to vary depending on the vascular bed in question.

Because of the potent effects of endothelins on renal blood flow [7], endothelin receptor antagonists may offer potential new therapies for renal diseases in which vasoconstriction may play a role. For example, ET<sub>A</sub>-selective and mixed antagonists have been shown to improve the renal blood flow and glomerular filtration rate in animal models of cyclosporine-induced renal failure [21, 22]. SB 209670, a nonselective endothelin receptor antagonist, has been found in prior animal studies to increase renal blood flow after radiocontrast administration [9] and thus was evaluated in the present study for the prevention of radiocontrast nephrotoxicity in patients undergoing cardiac angiography.

In this study, the mean increase in serum creatinine concentration was significantly higher in patients who received SB 209670 compared with those who received placebo. Similarly, the incidence of radiocontrast nephrotoxicity was not reduced by the use of SB 209670 in patients with pre-existing renal dysfunction. In contrast, the incidence of radiocontrast nephrotoxicity at 48 hours after radiocontrast administration was significantly higher in patients who received SB 209670 compared with patients who received placebo (56 vs. 29%, respectively).

Importantly, the negative effect of SB 209670 was apparent in both diabetic and non-diabetic patients who received the endothelin receptor antagonist. Although diabetic patients who were treated with SB 209670 had a significantly higher increase in serum creatinine and...
The present study involved patients with significant chronic renal insufficiency before cardiac angiography [mean serum creatinine = 2.7 ± 1.0 mg/dL (242.3 ± 92.8 μmol/L)], including 63% with diabetes mellitus. In this population, the response of the renal vasculature to endothelin and thus endothelin receptor antagonism may be attenuated or abnormal. Although there was a higher incidence of hypotension in patients treated with SB 209670 and, consequently, possible renal medullary ischemia, the mean increase in serum creatinine for patients with this adverse effect was less than for patients who did not have hypotension. Finally, at higher concentrations, SB 209670 has been found to block ET<sub>B</sub> receptors [23], thus inhibiting any potential vasodilatory effect of endothelin and possibly increasing plasma levels of endothelin [24].

Two broader questions are also raised by the results of this study: (1) the actual role of endothelin in the pathogenesis of radiocontrast nephrotoxicity; and (2) the potential benefit of any vasodilator therapy for reducing the risk of this complication. In animal models of radiocontrast nephrotoxicity, endothelin receptor antagonists increased renal blood flow and reduced renal vascular resistance after radiocontrast administration only when the production of renal prostaglandin was concomitantly inhibited [9, 10]. Thus, the interactions of multiple vasodilatory and vasoconstrictor influences likely determine whether radiocontrast nephrotoxicity occurs. Furthermore, the present study evaluated a mixed ET<sub>A</sub> and ET<sub>B</sub> receptor antagonist, and it is unknown whether selective ET<sub>A</sub> blockade may be beneficial in preventing radiocontrast nephrotoxicity. Despite these considerations, the lack of benefit of SB 209670 on the incidence of radiocontrast nephrotoxicity raises questions as to the role of endothelin in the pathogenesis of radiocontrast nephrotoxicity.

Other vasodilator agents, especially calcium channel antagonists and low-dose dopamine, have previously been evaluated for reducing the risk of radiocontrast nephrotoxicity. In two small studies involving a total of 65 patients, nifedipine and nitrendipine were found to increase renal blood flow and preserve the glomerular filtration rate after intravascular radiocontrast administration [25, 26], yet clinical outcome measures, such as the incidence of radiocontrast nephrotoxicity, were not evaluated. Low-dose dopamine infusion has also been observed to increase renal blood flow but was associated with a higher incidence of radiocontrast nephrotoxicity in diabetic patients [27, 28]. It has been hypothesized that vasodilators may primarily affect renal cortical blood vessels, resulting in an intrarenal “steal” phenomenon, which worsens renal medullary ischemia [28]. Thus, despite beneficial effects on renal hemodynamics, the potential role of vasodilator agents in reducing the risk of radiocontrast nephrotoxicity remains unproved. Our results further emphasize the discrepancy between surrogate markers of renal function, such as renal blood flow and glomerular filtration rate, and clinical outcome.

Finally, the group of patients in our study who received intravenous saline and placebo had an incidence of radiocontrast nephrotoxicity of 29%. This rate is somewhat higher than that reported in a recent study comparing intravenous saline alone to diuretic therapy plus saline, which used the same definition and observed an 11% incidence of radiocontrast nephrotoxicity in the saline-alone group [15]. However, the present study included patients with higher baseline serum creatinine concentrations and a higher percentage with diabetes mellitus. In addition, although the mean total duration of hydration in our placebo group was 24 hours, the duration of hydration before radiocontrast administration was more variable compared with the prior study [15]. At present, intravenous saline remains the most effective measure for reducing the risk of radiocontrast nephrotoxicity, although the optimal amount of hydration is not known.

In conclusion, the use of an intravenous mixed endothelin receptor antagonist did not reduce the risk of radiocontrast nephrotoxicity in patients with significant pre-existing renal dysfunction undergoing cardiac angiography. Rather, patients treated with this agent and intravenous hydration had a significantly higher incidence of radiocontrast nephrotoxicity compared with patients treated with intravenous hydration alone. In the future, patients treated with this novel class of therapeutic agents may require close observation for the development of nephrotoxicity after radiocontrast administration. Further studies of therapies for the prevention of
radiocontrast nephrotoxicity are needed and should focus on the clinical outcome of patients at high risk for this complication.

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APPENDIX

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