Effects of treatment with lispro and neutral protamine Hagedorn insulins on serum fructosamine and postprandial blood glucose concentrations in dogs with clinically well-controlled diabetes mellitus and postprandial hyperglycemia

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OBJECTIVE
To assess effects of basal-bolus insulin treatment (BBIT) with lispro and neutral protamine Hagedorn (NPH) insulins, compared with NPH insulin alone, on serum fructosamine concentration (SFC) and postprandial blood glucose concentration (BGC) in dogs with clinically well-controlled diabetes mellitus and postprandial hyperglycemia fed a high insoluble fiber–content diet.

ANIMALS
6 client-owned dogs with diabetes mellitus.

PROCEDURES
Blood samples were collected for BGC and SFC measurement in hospitalized dogs just before feeding and routine SC NPH insulin administration (time 0); samples were collected for BGC measurement every 30 minutes for 2 hours, then every 2 hours for up to 10 additional hours. Postprandial hyperglycemia was identified when BGC 30 minutes after insulin administration exceeded BGC at time 0 or the 1-hour time point. For BBIT, owners were instructed to continue NPH insulin administration at the usual dosage at home (q 12 h, with feeding) and to administer lispro insulin (0.1 U/Kg, SC) separately at the time of NPH injections. Two weeks later, SFC and BGC measurements were repeated; results at the start and end of the study were compared statistically.

RESULTS
Median SFC was significantly higher at the start (400 μmol/L) than at the end (390 μmol/L) of the study. Median 1-hour (313 mg/dL) and 1.5-hour (239 mg/dL) BGC measurements at the start of the study were significantly higher than those at the end of the study (117 and 94 mg/dL, respectively).

CONCLUSIONS AND CLINICAL RELEVANCE
In this sample of dogs with well-controlled diabetes mellitus, addition of lispro insulin to an existing treatment regimen of NPH insulin and dietary management significantly decreased postprandial BGCs. Further study of BBIT for dogs with diabetes mellitus is warranted. (*Am J Vet Res* 2020;81:153–158)

The use of several insulin preparations, including SC administration of NPH insulin for dogs with uncomplicated diabetes mellitus and IV administration of lispro insulin for dogs with diabetic ketoacidosis has been described.[1,2] However, a treatment protocol that involves both NPH and lispro insulins is a mainstay of diabetes mellitus treatment in human patients[3–5] that, to the authors' knowledge, has not yet been reported for dogs.

ABBREVIATIONS

BBIT	Basal-bolus insulin treatment
BGC	Blood glucose concentration
NPH	Neutral protamine Hagedorn
PPH	Postprandial hyperglycemia
SFC	Serum fructosamine concentration

Physiologic insulin secretion is comprised of 2 phases. In dogs, the first phase of insulin secretion begins 2 to 4 minutes after glucose stimulation, peaks approximately 8 to 10 minutes after this stimulation, and then plateaus.[6] The second phase of insulin secretion develops approximately 20 minutes after glucose stimulation and contributes to longer duration of the insulin plateau.[6] Basal-bolus insulin treatment comprises SC administration of a rapid-onset, short-duration insulin such as lispro at the time of meals to help address PPH by mimicking the first phase of insulin secretion and a longer-acting insulin such as NPH to mimic the basal phase of insulin secretion.[3–5] One of the goals of BBIT is to decrease the likelihood of long-term diabetes mellitus complications associ-

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ated with PPH. In human patients with diabetes mellitus, decreased frequency and magnitude of PPH is associated with decreased risk of vascular disease, retinopathy, and glomerulopathy as well as improved overall glycemic control and quality of life.[7–11]

The study reported here was designed as a preliminary (pilot) investigation to evaluate the feasibility of BBIT with NPH and lispro insulins and assess the effects of this treatment regimen, compared with NPH insulin administration alone, on SFC and postprandial BGC in dogs with clinically well-regulated diabetes mellitus and PPH that were fed a commercial diet with high insoluble fiber content.

Materials and Methods

Dogs

Dogs were enrolled in the study from the patient population of the University of Pennsylvania Ryan Veterinary Hospital. All dogs with diabetes mellitus that had routine 10- to 12-hour serial BGC measurements between May 2, 2011, and October 31, 2014, were screened for possible enrollment. To be included in the study, dogs were required to have clinically well-regulated diabetes mellitus. The condition was defined as clinically well regulated when the following conditions were met throughout the 4 weeks preceding the day of enrollment: no polyuria, polydipsia, polyphagia, or change in body weight; no new physical examination findings; and no change in insulin dosage. Additional inclusion criteria were that the dog was undergoing treatment with NPH insulin[a] at a dosage of ≤ 1.0 U/kg, SC, every 12 hours; that it was solely fed 1 designated diet high in insoluble fiber and complex carbohydrate content (canned, dry, or both)[b] at a fixed amount twice daily for ≥ 4 weeks prior to the screening date; that PPH was detected by BGC measurement on the enrollment date; and that the owner provided informed consent for inclusion of the dog in the study and was willing to return the dog to the hospital for serial 10- or 12-hour BGC measurements at the end of the 2-week study.

Dogs with a diagnosis of systemic disease other than diabetes mellitus, sexually intact female dogs, and dogs receiving medications that could influence insulin action were excluded from the study. Medications that warranted study exclusion included oral, topical, or ophthalmic corticosteroid-containing preparations. Dogs that did not readily eat an entire meal at the hospital after the first blood sample collection were also excluded. The study and the client consent form were approved by the University of Pennsylvania Institutional Animal Care and Use Committee.

Procedures

On the day of enrollment, dogs were admitted to the hospital. A venous blood sample (3 mL) was collected for hematologic testing, including a CBC,[c] serum biochemical analysis,[d] and measurement of SFC.[e] Urinalysis by dipstick testing[f] and aerobic bacterial culture with microbial identification and antimicrobial susceptibility testing[g] were completed for a urine sample obtained by cystocentesis. A venous blood sample was collected for BGC measurement just prior to feeding the designated diet and administering NPH insulin (time 0). The NPH insulin was administered SC at the same dose that had been given for ≥ 4 weeks previously. Additional samples were collected for BGC measurement of all dogs 0.5, 1, 1.5, 2, 4, 6, 8, and 10 hours after insulin injection. A sample was collected for BGC measurement 12 hours after insulin administration if the owner consented to leave the dog at the hospital for the additional 2 hours. The BGC was measured in whole blood immediately after each sample collection with a single designated glucometer[h] validated for use with canine blood samples.[12] A dog was identified as having PPH if its BGC at the 30-minute time point was greater than its BGC at time 0 or at the 1-hour time point.

All serial BGC measurements were performed at the hospital, but dogs spent the 2-week study period at home with BBIT performed by the owners. Once PPH was confirmed in a dog that met all other inclusion criteria and the first set of serial BGC measurements was completed, lispro insulin[i] (0.1 U/kg, SC, q 12 h) was prescribed, to be administered as a separate injection at the time of NPH insulin administration starting that evening. The dosage of NPH insulin, the fixed amount of food fed, and the times of feeding and insulin administration remained unchanged. Both insulin injections were administered to each dog every 12 hours, once between 6 AM and 8 AM and once between 6 AM and 8 PM. Both injections were given in the dorsal aspect of the neck. Lispro and NPH insulin injections were administered within seconds of each other in no specified order. Owners were required to keep a 2-week daily log of their pet's drinking and urination habits, appetite, and activity level and to note any indication of weakness, disorientation, collapse, or seizures. Owners were instructed to contact the researchers at any time if they had any concerns or questions.

Dogs were reevaluated on day 14, with the day of enrollment considered day 1. The same protocol of serial BGC measurements that was performed at the time of enrollment was followed on day 14, at which time dogs received both NPH and lispro insulins, and an additional blood sample was collected for SFC measurement. The dog's clinical history and the completed daily log were reviewed, and a physical examination was performed. Hypoglycemia was defined as a BGC < 50 mg/dL as measured in whole blood samples with the designated glucometer. This value was chosen because whole blood measurements with this specific glucometer were ≥ 25 mg/dL lower than serum BGC measured on the in-house automated biochemistry analyzer at the institution's clinical laboratory, and the reference range for serum BGC at the clinical laboratory was 65 to 100 mg/dL.[12,d] The study[12] in which this

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difference in BGC measurements was found included 96 blood samples from dogs, but no samples were from dogs with hypoglycemia. Because hypoglycemia can be fatal, a measure of caution was introduced and values < 50 mg/dL were considered to indicate hypoglycemia. The laboratory reference range for SFC was 200 to 375 µmol/L.

Statistical analysis

Results were summarized as median and range, and nonparametric statistical analysis was performed for all tests because of the small sample size. The Friedman test was performed to determine whether there was a difference in median BGC across all 10 postinjection time points (up to 12 hours after insulin administration) between the NPH insulin–only and BBIT protocols. The Friedman test was followed by the Wilcoxon signed rank test, which was used for pairwise comparison of median BGC at each postinjection time point at enrollment and 2 weeks later. The Wilcoxon signed rank test was also used for pairwise comparisons of median BGC at consecutive time points within each treatment protocol, and comparison of median SFC at enrollment versus 2 weeks later. All statistical evaluations were performed with a statistical software package.[j]

Results

Six dogs were enrolled in the study, and all enrolled dogs completed the study. Median age of the dogs was 10.7 years (range, 6 to 13.5 years). The diagnosis of diabetes mellitus had been made a median of 1 year (range, 6 months to 1 year) prior to study enrollment. Four of the 6 dogs were spayed females, and 2 were castrated males; 2 were mixed-breed dogs, and there was 1 dog each of the following breeds: Pug, Jack Russell Terrier, Shih Tzu, and Pomeranian.

The 2-week daily log completed by owners indicated that all dogs had subjectively normal drinking and urination habits, appetites, and activity levels, and none of the dogs had signs of weakness, disorientation, collapse, or seizures. The median NPH insulin dose at the time of enrollment and throughout the study was 0.66 U/kg (range, 0.35 to 0.97 U/kg), given SC every 12 hours. Three dogs were fed a mixture of dry and canned study-designated diet, 2 dogs were fed canned study-designated diet, and 1 dog was fed dry study-designated diet only. All dogs ate their entire meal at the hospital just before insulin administration on the day of enrollment and 2 weeks later. The CBC, serum biochemical analysis, and urinalysis results were consistent with findings reported in dogs with diabetes mellitus.[13] There was no bacterial growth on aerobic bacterial culture of urine samples.

One hundred and seventeen BGCs were analyzed. The BGC in all 6 dogs was measured at all time points, except at 12 hours; a sample was collected at this time point from 4 dogs at the start of the study (day 1) and 5 dogs at the end of the study (day 14). Friedman test results indicated a significant (P = 0.002) difference in median BGC between the NPH insulin–only and BBIT protocols **(Table 1)**. Pairwise testing revealed that median BGC at the 1-hour postinjection time point was significantly (P = 0.028) lower when dogs received BBIT (117 mg/dL), compared with median BGC at 1 hour when the same dogs were treated with NPH insulin alone (313 mg/dL). Similarly, median BGC at the 1.5-hour time point was significantly (P = 0.028) lower when dogs received BBIT (94 mg/dL) than when they were given NPH insulin alone (239 mg/dL). At the 10-hour time point, median BGC was also significantly (P = 0.035) lower when dogs had BBIT (91 mg/dL) than when they received NPH insulin alone (213 mg/dL). No other significant differences in median BGC were detected between protocols.

Within the NPH insulin–only treatment, median BGC 30 minutes after injection (378 mg/dL) was significantly (P = 0.028) higher than that at 1 hour (313 mg/dL), and the result at 1 hour was significantly (P = 0.028) higher than that at 1.5 hours (239 mg/dL), which was significantly (P = 0.028) higher than the result at 2 hours (191 mg/dL; Table 1). Within the BBIT, median BGC at time 0 (290 mg/dL) was significantly (P = 0.046) higher than that at 0.5 hours (247 mg/dL), and the median measurement at 0.5 hours was significantly (P = 0.028) higher than that at 1 hour (117 mg/dL). Median BGCs did not differ significantly between any other consecutive time points within treatments.

Table 1—Comparison of median (range) serially measured BGCs in 6 client-owned adult dogs immediately before (time 0) and at predetermined time points after feeding and insulin administration in a preliminary study to evaluate effects of BBIT with lispro and NPH insulins, compared with NPH insulin administration alone, on SFC and postprandial BGC in dogs with clinically well-controlled diabetes mellitus and PPH that were fed a high insoluble fiber–content diet.

	BGC (mg/dL)	
Time (h)	NPH insulin	BBIT
0	337 (246–418)	290 (160–438)*
0.5	378 (263–490)*	247 (50–391)*†
1	313 (187–376) *†§	117 (42–307)†
1.5	239 (166–332)†‡§	94 (48–197)
2	191 (61–301)‡	112 (48–186)
4	136 (50–293)	103 (71–261)
6	127 (62–279)	94 (44–311)
8	191 (74–303)	122 (39–365)
10	213 (66–320)§	91 (46–320)
12	254 (108–287)	96 (51–297)

Dogs received NPH insulin alone at the routinely administered dose, SC, on the day of study enrollment (day 1) and then underwent BBIT (NPH insulin at the routinely administered dose, SC, q 12 h, plus lispro insulin at 0.1 U/kg, SC, at the same time as NPH insulin administration) for 14 days, with serial BGC measurements repeated on day 14. Not all dogs had a 12-hour sample collected (n = 4 and 5 on days 1 and 14, respectively). The BGC was measured in whole blood samples with a single designated glucometer. Results differed significantly (Friedman test; P = 0.002) between treatment protocols; significant (P < 0.05) differences are indicated for pairwise comparisons.

*†‡Within a column, median values with the same symbol differ significantly. §Median value is significantly (P < 0.05) different from that of BBIT at the same time point.

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Median SFC was significantly (P = 0.046) lower when dogs received BBIT (390 µmol/L; range, 253 to 486 µmol/L) than when they were treated with NPH insulin alone (400 µmol/L; range, 289 to 624 µmol/L). Owners and clinicians observed no clinical signs suggestive of hypoglycemia during the study. However, hematologic evidence of hypoglycemia was noted in 7 of 117 (6%) samples from 3 of 6 dogs during serial BGC measurement on day 14 of BBIT. Median glucometer-measured BGC in these 7 samples was 46 mg/dL (range, 39 to 48 mg/dL). There were no reported changes in drinking and urination habits, appetite, activity level, or other clinical signs for any dogs during the 2-week study period. There were also no owner-reported problems related to the BBIT protocol, and all owners adhered to the study protocol as instructed.

Discussion

In the present study, BBIT with NPH and lispro insulins in dogs was associated with significantly lower BGCs 1 and 1.5 hours after feeding, compared with results when the same dogs were treated with NPH insulin alone. Furthermore, the pattern of changes in BGC after feeding and insulin administration differed between the 2 treatment protocols. With NPH insulin treatment alone, there was an initial increase in median BGC as expected in accordance with case selection criteria, although the difference in these values between time 0 (immediately prior to injection) and 0.5 hours after injection was not significant. With the BBIT protocol, there was a significant decrease in median BGC between time 0 and the 0.5-hour time point. The difference in BGC values between the NPH insulin–only and BBIT protocols 1 and 1.5 hours after injection was not only statistically significant but also clinically meaningful. The utility of serial BGC measurements as a monitoring tool for dogs with diabetes mellitus has come into question.[14] However, the changes in BGC of dogs in the present study were reflected in significantly decreased median SFC 2 weeks after lispro insulin administration was added to the treatment protocol. This suggested that reducing the magnitude or frequency (or both) of PPH improves overall glycemic control in dogs with clinically well-regulated diabetes mellitus.

In people, a decrease in the frequency and magnitude of PPH is associated with improved glycemic control and fewer long-term diabetes mellitus–related complications including vascular disease, retinopathy, and glomerulopathy.[7-10] Dogs with diabetes mellitus are also at risk for some of these long-term complications. Although atherosclerosis is not frequently diagnosed in dogs, dogs with atherosclerosis are > 50 times as likely to have concurrent diabetes mellitus, compared with dogs without atherosclerosis.[15] Additionally, systemic hypertension is common in dogs with diabetes mellitus and was reported in 23 of 50 (46%) dogs with diabetes mellitus in a previous study.[16] Although the long-term clinical importance of atherosclerosis and hypertension in dogs with diabetes mellitus is not known, these 2 factors increase the risk of cardiovascular disease in humans and could contribute to cardiovascular disease in dogs.[17] Another study[18] identified retinal disease in 11 of 52 (21%) dogs with diabetes mellitus, compared with only 1 of 174 (0.6%) dogs without diabetes mellitus. Renal glomerular disease in dogs with diabetes mellitus is also well documented, and an association between atherosclerosis and glomerular disease has been reported in dogs.[19,20] Larger studies of greater duration are needed to investigate the use of BBIT in a more diverse group of dogs, including dogs with concurrent illness, to determine whether the observed effect of the BBIT on postprandial BGCs of dogs in the present study is consistent and can decrease the risk of these comorbidities in dogs with diabetes mellitus.

In the present study, the significant decrease in SFC measured after 2 weeks of BBIT indicated that BGCs were decreased throughout the study period and not only at the end of the study on day 14 when the follow-up serial BGC measurements were performed. The SFC was not used to determine whether a dog had well-regulated diabetes mellitus because only dogs with well-regulated diabetes mellitus were enrolled in the study. The change in SFC at the end of the study, although statistically significant, was not deemed clinically important.

Our study sample was carefully selected to include dogs with clinically well-regulated diabetes mellitus that still had PPH. This sample of dogs was chosen in an attempt to focus the study on PPH and the effect of BBIT on postprandial BGCs in patients with this finding. Dietary measures are commonly used as a means to mitigate PPH. The diet used in our study was chosen because the high insoluble fiber and complex carbohydrate content improves glycemia control,[21] but results of a previous study[1] indicated that, when treated with NPH insulin and this diet, some dogs with otherwise well-regulated diabetes mellitus still have PPH. In the clinical setting, veterinarians and owners will likely prefer to improve glycemic control with dietary management first and introduce a BBIT only if PPH persists despite nutritional management. A homogenous population of dogs was sought for the exploratory study reported here in an effort to isolate the effects on postprandial BGCs when lispro insulin is added to the treatment protocol of dogs receiving NPH insulin and to minimize the influence of various diets, other illnesses, and medications on the results. However, in evaluating results of this study, it should be considered that dogs with diabetes mellitus frequently have other medical conditions, and their diabetes mellitus is not always well regulated.[13]

For purposes of the present study, a dog was defined as having PPH if its BGC at 0.5 hours after feeding and insulin administration was greater than its BGC at time 0 or the 1-hour time point. This definition was chosen on the basis of results of the aforementioned

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study[1] of dogs with well-regulated diabetes mellitus that were being treated with the same diet and with NPH insulin. In that study,[1] the peak of PPH occurred 30 minutes after feeding and insulin administration, and median time to return to BGC measured at the time of feeding and insulin administration in dogs with PPH was 0.7 hours.[1] However, it is possible that a mild increase in BGC is to be expected and that it is not necessarily pathological. With the availability of continuous glucose monitors, more data could become available to better define PPH in dogs.[22]

Only one BBIT regimen was investigated in the study reported here. Other rapid-onset, short-duration insulin products such as aspart and glulisine insulins are also used for the bolus component of BBIT in human patients.[23,24] Similarly, other intermediate- or long-duration insulin products such as glargine, detemir, and degludec are used to mimic the basal second phase of insulin secretion.[3–5,23] Data suggest that in people, glargine is more effective than NPH as a basal insulin for BBIT, in that glargine offers improved glycemic control with less risk of hypoglycemia.[4,25] Future studies in dogs will be needed to determine the best combination of insulin products for BBIT.

Nonclinical hypoglycemia was identified on the basis of BGCs in 7 of 117 (6%) blood samples during serial testing, and the lowest BGC detected was 39 mg/dL. However, results of another study[1] indicated that in dogs, whole blood BGC measurements obtained with this same point-of-care glucometer are ≥ 25 mg/dL lower than plasma or serum BGC measurements. Therefore, the lowest BGC measured in this study on whole blood with a point-of-care glucometer (39 mg/dL) likely reflected a value of approximately 64 mg/dL or greater measured on the automated biochemistry analyzer. This could explain why the low BGCs noted did not result in clinical signs. Nevertheless, every measure to avoid hypoglycemia should be taken. Therefore, for future studies of dogs with well-regulated diabetes mellitus treated with NPH insulin and the study-designated diet, our findings suggested that lispro administration should be started at a lower dosage of 0.075 U/kg, SC, every 12 hours when added to NPH insulin for BBIT. For future studies of dogs with poorly regulated diabetes mellitus or concurrent illness, or of dogs fed another diet, a lispro dosage of 0.1 U/kg, SC, every 12 hours in combination with NPH insulin could be appropriate. Communication with the owner, monitoring of clinical signs, and serial BGC measurements performed approximately every 2 weeks would be needed for any lispro dosage chosen, with dose adjustments as needed.

The finding that median BGC 10 hours after feeding and insulin administration was significantly lower when dogs underwent BBIT, compared with results for the same dogs when they received NPH insulin alone, was unexpected because the duration of lispro insulin action after SC administration in people is 4 to 6 hours.[26] A possible explanation is that because the addition of lispro insulin resulted in lower BGC in the first 90 minutes after injection, NPH insulin was acting on an already reduced BGC, resulting in a significant difference at the 10-hour time point. The magnitude of the difference in BGC between the 2 treatment regimens at the 12-hour time point appeared similar to that at 10 hours; however, fewer samples were available for analysis at the final time point, in which the difference was nonsignificant. It is possible that with a larger sample size, significant differences in BGC could also be detected 12 hours after feeding and insulin administration with this protocol. These findings suggested that reduction of the NPH dose may be warranted in some dogs, and this should be investigated further.

One of the limitations of the present study was that correction for multiple comparisons was not performed. The goal of multiple-comparisons correction is to decrease the possibility of a significant *P* value that may arise owing to chance when performing a large number of tests. However, an unfortunate outcome of correcting for multiple comparisons is that such corrections increase the possibility that a true significant difference is not detected. In a small, proof-of-concept, exploratory study intended to serve as a basis for future research, it is paramount to avoid such false-negative results.[27] This preliminary study had several other limitations. First, it was a small study that might not have had sufficient power to detect all of the differences in BGCs analyzed. Second, the study focused on a very homogenous group of well-regulated dogs with diabetes mellitus that were fed and treated with insulin in a hospital setting and therefore, the study findings might not be generalizable to clinical situations in which dogs have concurrent disorders and are fed at home. Another limitation was that the statistically significant decrease in SFC was difficult to interpret in dogs with clinically well-regulated diabetes mellitus that had no changes in clinical signs during the 2-week study period. Additionally, the short-term study was not designed to investigate possible associations between changes in BGC resulting from BBIT and long-term comorbidities related to diabetes mellitus. Furthermore, in lieu of a control group, dogs served as their own controls. Finally, although all dogs were fed the study-designated diet, some received the dry formulation and others received the canned formulation or a mix of canned and dry formulations. This variability in diet could have influenced the extent and duration of PPH, especially because there are important differences in the fat and fiber contents between these diet formulations, and this is a subject that warrants further investigation for dogs undergoing BBIT. Overall, results of this preliminary investigation of the use of NPH insulin, lispro insulin, and a designated diet for treatment of dogs with clinically well-regulated diabetes mellitus showed that a BBIT protocol is feasible for dogs and supported that BBIT results in better control of PPH than NPH insulin administration alone.

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Footnotes

a. Humulin-N, Eli Lily and Co, Indianapolis, Ind.
b. Prescription Diet w/d, Hill's Pet Nutrition Inc, Topeka, Kan.
c. Celldyne 3500, Abbott Laboratories, Abbott Park, Ill.
d. Kodak Ektachem 250, Eastman Kodak Co, Rochester, NY.
e. Fructosamine SPOTCHEM EZ, Heska Corporation, Loveland, Colo.
f. N-Multistix SG, Bayer Corp, Elkhart, Ind.
g. Microscan WalkAway SI 40, Siemens Healthcare Diagnostics Inc, Sacramento, Calif.
h. Accu-Check Aviva, Roche Diagnostics, Indianapolis, Ind.
i. Humalog, Eli Lily and Co, Indianapolis, Ind.
j. Stata, version 14.0 for Mac, Stata Corporation, College Station, Tex.

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