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Sevelamer Hydrochloride Dose-Dependent Increase in Prevalence of Severe Acidosis in Hemodialysis Patients: Analysis of Nationwide Statistical Survey in Japan

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Abstract: Metabolic acidosis has a negative impact on prognosis of dialysis patients. The aim of this study was to determine the prevalence of severe metabolic acidosis in dialysis patients treated with sevelamer hydrochloride. In 2004, a nationwide survey (101 516 dialysis patients) was conducted by the Japanese Society for Dialysis Therapy. We analyzed 32 686 dialysis patients whose bicarbonate levels were measured in the survey. Sevelamer hydrochloride was prescribed to 9231 dialysis patients while 23 455 dialysis patients were not prescribed sevelamer hydrochloride. In the present study, we defined severe acidosis as bicarbonate <15.8 mmol/L. The mean serum bicarbonate level correlated significantly and negatively with the daily dose of sevelamer hydrochloride ($R^2 = 0.806$, $P < 0.0001$).

Logistic regression analysis indicated that the percentage of patients with severe acidosis increased significantly with increased dose of sevelamer hydrochloride ($R^2 = 0.885$, $P < 0.00001$). The estimated doses of sevelamer hydrochloride associated with severe acidosis in 10% and 15% of patients were 3.5 g/day (95% confidence interval [95%CI], 2.8-4.4) and 7.7 g/day (95%CI = 5.9-10.9), respectively. Severe acidosis was noted in 4.5% of patients who were not treated with sevelamer hydrochloride and in 16.1% of patients treated with sevelamer hydrochloride at ≥ 5.25 g/day ($P < 0.0001$). The results call for careful monitoring of serum bicarbonate level in hemodialysis patients treated with sevelamer hydrochloride. **Key Words:** Dialysis, Metabolic acidosis, Prognosis, Sevelamer hydrochloride.

Hyperphosphatemia is common in dialysis patients and can cause extensive calcification in the cardiovascular system with a negative impact on prognosis and quality of life (1). The annual mortality rate of patients undergoing dialysis in Japan is nearly 10%, and cardiovascular disease is the cause of death in approximately 40% of such patients (2). Clinicians advise these patients to avoid foods with high phosphorus content, and often use phosphate binders to control hyperphosphatemia in these patients. Aluminum- or calcium-based phosphate binders have been used, but the former group of binders was found to cause aluminum encephalopathy, and accordingly had been listed as contraindicated for

dialysis patients in Japan. On the other hand, the use of calcium-based phosphate binders is often associated with calcium overload with subsequent calcification of the cardiovascular system.

Sevelamer hydrochloride was introduced as a non-aluminum, non-calcium phosphate binder and is recommended for use to improve the prognosis of dialysis patients (3). Furthermore, sevelamer hydrochloride is also known to adsorb LDL-cholesterol and thus have lipid-lowering properties. Several other reports indicated that sevelamer hydrochloride can inhibit the progression of coronary and aortic calcification in HD patients compared with calcium-based binders (4,5). Based on these studies, the use of sevelamer hydrochloride is expected to reduce cardiovascular mortality in dialysis patients.

Sevelamer hydrochloride contains chlorine, and any chlorine load could potentially result in reduction of bicarbonate and the development of hyperchloremic acidosis. In this regard, statistically

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significant but slight decline in bicarbonate level after administration of sevelamer hydrochloride has been reported (6–8).

In 2004, a nationwide survey of 101 516 dialysis patients was conducted by the Japanese Society for Dialysis Therapy. The survey found low bicarbonate levels in patients treated with high doses of sevelamer hydrochloride, though the study lacked statistical analysis (9).

Sevelamer carbonate was developed recently by Genzyme Co. as equivalent to sevelamer hydrochloride. Sevelamer carbonate is an anion exchange resin with polymeric structure similar to that of sevelamer hydrochloride, in which carbonate replaces chloride as the anion. A randomized, double-blind, crossover study indicated that sevelamer carbonate does not cause metabolic acidosis (10). Sevelamer carbonate has been released into the market in the United States and some countries in Europe, but not in Japan.

We hypothesized that a proportion of patients treated with high doses of sevelamer hydrochloride can develop severe acidosis. It is important to assess the relationship between sevelamer hydrochloride and severe acidosis quantitatively. The present study analyzed statistically the data of the 2004 nationwide survey to examine the prevalence of severe metabolic acidosis in patients on HD and peritoneal dialysis treated with high doses of sevelamer hydrochloride. This is the first report of the dose response relationship between sevelamer hydrochloride and development of severe metabolic acidosis capable of impairing the prognosis of dialysis patients.

PATIENTS AND METHODS

Patients and data

The Japanese Society for Dialysis Therapy (JSDT) has been conducting an annual statistical survey of dialysis facilities across the country since 1968. As

TABLE 1. Profile of patients

Total number of patients	32 686 (100%)
Sex	
Males	19 777 (60.5%)
Females	12 909 (39.5%)
Age	
<65 years	17 095 (52.3%)
≥65 years	15 590 (47.7%)
Treatment type	
Hemodialysis	24 408 (74.7%)
CAPD	453 (1.4%)

For hemodialysis patients, the duration of dialysis was more than 1 year, performed three times a week. CAPD, continuous ambulatory peritoneal dialysis.

TABLE 2. Number of patients treated with the indicated doses of sevelamer hydrochloride

Dose (g/day)	N
<0.75	161
≥0.75 to <1.50	1197
≥1.50 to <2.25	2063
≥2.25 to <3.00	1316
≥3.00 to <3.75	1994
≥3.75 to <4.50	601
≥4.50 to <5.25	774
≥5.25 to <6.00	140
≥6.00 to <6.75	545
≥6.75 to <7.50	71
≥7.50 to <8.25	185
≥8.25 to <9.00	8
≥9.00	176

part of this activity, a nationwide statistical survey of 3932 dialysis facilities was carried out at the end of 2004, and a response was received from 3882 facilities (98.7%) on the management of 101 516 dialysis patients. The 2004 survey included sevelamer hydrochloride use and serum bicarbonate level, although the latter was measured in 32.3% of the patients.

Permission from the JSDT was secured to analyze the data of the 2004 survey. The data tables included the dose of sevelamer hydrochloride and serum bicarbonate level/extent of acidosis. The present study was conducted using the data of 32 686 patients whose bicarbonate levels were measured in the 2004 JSDT survey (Table 1).

Among these patients, 9231 patients were treated with sevelamer hydrochloride, while 23 455 were not treated with sevelamer hydrochloride. Sevelamer hydrochloride (Renagel 250 mg tablets; Chugai Pharmaceutical Tokyo, or Phosblock 250 mg tablets; Kyowa Hakko Kirin, Tokyo, Japan) was prescribed at each hospital. The maximum dose of sevelamer hydrochloride specified in Japan is 9.0 g.

Arterial blood samples were collected before dialysis and analyzed in each hospital or laboratory. The mean serum bicarbonate level in the sevelamer hydrochloride group was 19.68 mmol/L. In contrast, the mean level of bicarbonate was 20.76 mmol/L in the group not treated with sevelamer hydrochloride. As shown in Table 2, 70% of patients were prescribed a daily dose of sevelamer hydrochloride of 0.75 to 3.75 g/day.

For the analysis of severity of acidosis according to age, sex and treatment modality, we divided the patients into six sevelamer hydrochloride dose groups (0, <1.5, ≥1.5 to <2.25, ≥2.25 to <3.0, ≥3.0 to <3.75, ≥3.75 to <5.25, and ≥5.25 g/day), each comprising at least 1000 patients. The percentage of patients treated with a dose of more than 6.75 g/day

was small. Furthermore, the number of patients treated by continuous ambulatory peritoneal dialysis (CAPD) was small.

Level of acidosis used in the present study

One study from the USA (11) indicated that bicarbonate concentration of ≥ 22 mEq/L was associated with less risk for death, whereas bicarbonate level < 17 mEq/L was associated with high death risk. However, in our study, these values were corrected because the day of the week in which blood tests are conducted in Japan are different from that followed in the above study. Blood from HD patients is tested at midweek in the USA, while it is carried out at the beginning of the week in Japan. Accordingly, serum bicarbonate level at the beginning of the week was corrected to midweek values (similar to the USA) by subtracting 1.2 mEq/L (mmol/L), similar to the Dialysis Outcome Practice Pattern Study (DOPPS) on bicarbonate level (12). Thus, bicarbonate levels of 22 and 17 mmol/L measured in this study in Japan were corrected to 20.8 and 15.8 mEq/L, respectively. Based on these values, we classified the patients into those with normal bicarbonate level (arterial blood bicarbonate ≥ 20.8 mmol/L), those with moderate acidosis (15.8 mmol/L \leq arterial blood bicarbonate < 20.8 mmol/L) and severe acidosis (arterial blood bicarbonate < 15.8 mmol/L).

Statistical analysis

Statistical significance was evaluated by Pearson's correlation coefficient and probit curve using Micro-

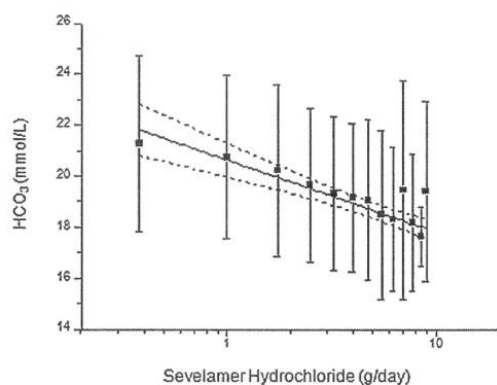


FIG. 1. Correlation between daily dose of sevelamer hydrochloride and serum bicarbonate level is shown. Data are mean \pm standard deviation (SD). The abscissa represents semi-log values of the raw data. Solid line: regression line; dashed lines: upper and lower limits of the 95% confidence interval. HCO_3^- : serum bicarbonate (mmol/L). $n = 13$, $R^2 = 0.806$, $P < 0.0001$.

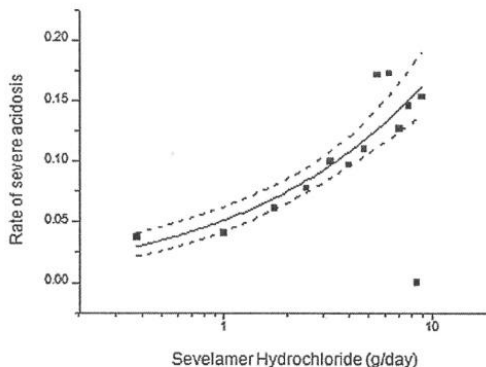


FIG. 2. Relationship between daily dose of sevelamer hydrochloride and percentage of patients with severe acidosis (serum bicarbonate < 15.8 mmol/L) is shown. Solid line: logistic (probit) curve; dashed lines: upper and lower limits of the 95% confidence interval. $n = 13$, $R^2 = 0.885$, $P < 0.00001$.

cal Origin v5.0 software (Microcal Software, Northampton, MA, USA) and Fisher's exact test using JUMP v9.0 software (SAS Institute, Cary, NC, USA). The probit curve is one of the logistic regression analyses and expresses the probability of occurrence and is generally used in toxicology for analysis of the LD50 values. In all analyses, a P -value of < 0.05 denoted the presence of a statistically significant difference.

RESULTS

Relation between dose of sevelamer and mean blood bicarbonate level

The mean blood bicarbonate level in the patients treated with sevelamer hydrochloride correlated significantly and negatively with the logarithm of sevelamer hydrochloride dose ($n = 13$, $R^2 = 0.806$, $P < 0.0001$, Fig. 1). According to this result, the mean bicarbonate level of 15.8 mmol/L corresponds to sevelamer hydrochloride dose of 51.6 g/day.

Relation between dose of sevelamer and probability of severe acidosis

There was a close logistic relationship between the dose of sevelamer hydrochloride and probable severe acidosis (probit curve, $n = 13$, $R^2 = 0.885$, $P < 0.00001$, Fig. 2). The rate of severe acidosis in patients treated with sevelamer hydrochloride was 5.7%. On the other hand, the rate of severe acidosis in patients who did not receive sevelamer hydrochloride was 4.5%. The estimated doses of sevelamer hydrochloride associated with severe acidosis in 10% and 15% of patients were 3.5 g/day (95% confidence

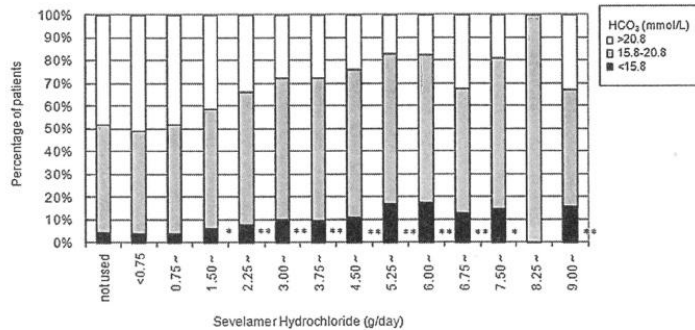


FIG. 3. Percentages of patients with the indicated level of serum bicarbonate, stratified according to the dose of sevelamer hydrochloride are shown. HCO_3^- serum bicarbonate (mmol/L). $n = 32\ 686$, * $P < 0.01$, ** $P < 0.0001$, compared with the untreated patients (by Fisher's exact test).

interval, 2.8–4.4) and 7.7 g/day (95% confidence interval, 5.9–10.9), respectively.

Distribution of acidosis and sevelamer hydrochloride dose

The percentage of patients with moderate and severe acidosis increased among patients treated with higher doses of sevelamer hydrochloride (Fig. 3). The percentages of patients with severe acidosis for each dose group, treated with sevelamer hydrochloride at ≥ 1.5 g/day, were significantly higher than untreated patients ($P < 0.05$, each), except those on 8.25–9.00 g/day ($n = 8$). We defined the dose of > 5.25 g/day as the high dose of sevelamer hydrochloride. The percentage of patients with severe acidosis was 16.1% among those treated with high dose of sevelamer hydrochloride. This rate was significantly higher than that of untreated patients (16.1% vs. 4.5%, $P < 0.0001$). Furthermore, the percentage of patients with severe and moderate acidosis among those treated with high dose of sevelamer hydrochloride (79.1%) was also significantly higher than in untreated patients (51.8%, $P < 0.0001$).

Severity of acidosis according to age, sex and treatment modality

The prevalence of acidosis in males and females was almost identical, and in those aged < 65 and ≥ 65 years of age. The prevalence of acidosis in both sexes and age groups tended to increase in a dose-dependent manner (data not shown). However, the percentage of patients who developed severe acidosis among those on CAPD was less than those on HD, and no dose-dependent effect was noted in the former group (Fig. 4).

DISCUSSION

Metabolic acidosis impairs nutritional state, bone metabolism, and prognosis of dialysis patients (13).

The US National Kidney Foundation recommends maintenance of total CO_2 level at ≥ 22 mEq/L (22 mmol/L) in dialysis patients for proper bone metabolism and nutrition (14). DOPPS showed that low (≤ 17 mEq/L) bicarbonate (total CO_2) levels were associated with increased risk for hospitalization and mortality (12).

Recently, Wu et al. (11) examined the relationship between predialysis serum bicarbonate levels and 2-year mortality rate in 56 385 patients on maintenance HD, and concluded that serum bicarbonate levels above 22 mEq/L were associated with lower death risk. The lowest adjustment mortality was associated with predialysis serum bicarbonate level of < 17 mEq/L.

Bicarbonate levels of 22 and 17 mmol/L are corrected to 20.8 and 15.8 mEq/L in Japanese patients, respectively, because blood samples from HD patients are tested at midweek in the USA, compared with at the beginning of the week in Japan. It should be noted that serum bicarbonate levels at the beginning of the week were corrected in DOPPS to midweek values (like the USA) by adding 1.2 mEq/L (mmol/L) to the measured value (12). The same approach was also followed in the present study.

What is the mechanism of sevelamer hydrochloride-induced acidosis? Brezina et al. (15) indicated that sevelamer hydrochloride induces acidosis by releasing hydrochloric acid during the process of adsorption with phosphate, bile acid, or bicarbonate within the small intestine.

Our previous retrospective study of HD patients (16) demonstrated that serum bicarbonate level, base excess, and pH decreased in a sevelamer hydrochloride dose-dependent manner in the absence of hyperchloremia (serum $\text{Cl}^- > 108$ mmol/L). Furthermore, the results also showed that the delta change in these parameters (before and after administration of sevelamer hydrochloride) increased in a dose-dependent

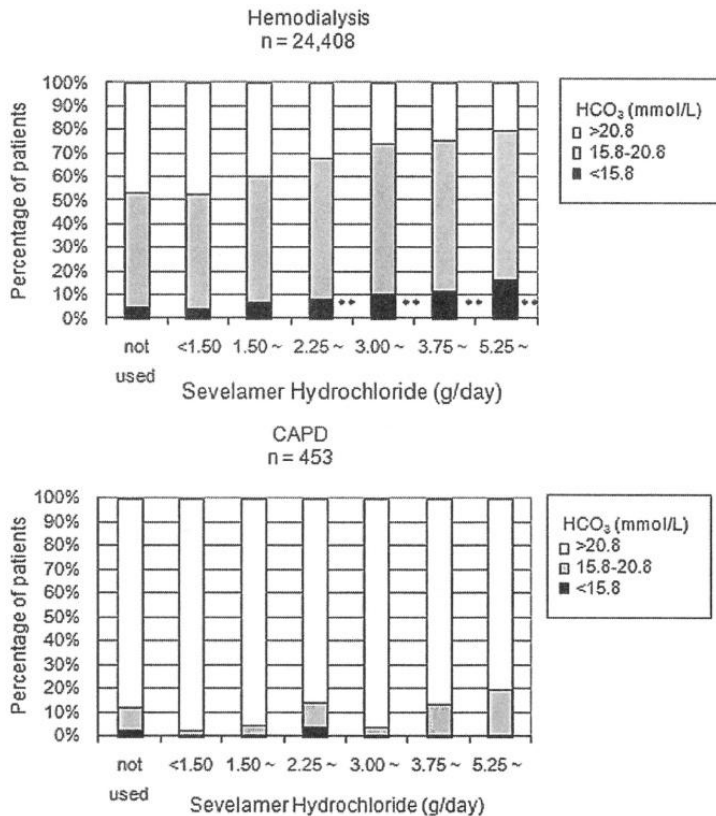


FIG. 4. Percentages of patients with the indicated level of serum bicarbonate, stratified according to the dose of sevelamer hydrochloride and treatment type (hemodialysis and continuous ambulatory peritoneal dialysis [CAPD]) are shown. HCO₃: serum bicarbonate (mmol/L). **P* < 0.05, ***P* < 0.0001, compared with the untreated patients (by Fisher's exact test). For hemodialysis patients, the duration of dialysis was more than 1 year, performed 3 times a week.

manner. In comparison, no aggravation of acidosis was seen in the control group.

Based on our data (16) and those of sevelamer hydrochloride pharmacokinetics (15), we speculate that sevelamer hydrochloride reacts with phosphate (H₃PO₄) through adsorption of phosphate ion (PO₄³⁻) and releases chlorine ion (Cl⁻) to produce hydrochloric acid (HCl). Phosphate is a weak acid while hydrochloric acid is a strong acid with almost 100% ionization, and accordingly hydrochloric acid induces more severe acidosis than phosphate.

In this study, we analyzed the data of the 2004 survey. Only small differences in the mean bicarbonate level and prevalence of severe acidosis were noted between sevelamer hydrochloride-treated and untreated patients (19.68 mmol/L vs. 20.76 mmol/L, and 5.7% vs. 4.5%, respectively). Though the mean blood bicarbonate level correlated strongly and negatively with the dose of sevelamer hydrochloride, a mean bicarbonate level 15.8 mmol/L would

correspond to sevelamer hydrochloride dose of 51.6 g/day (about 206 tablets a day). These results suggest that sevelamer hydrochloride does not seem to cause severe acidosis. However, the probit curve analysis indicated a close logistic relationship between the dose of sevelamer hydrochloride and severe acidosis, and that the estimated dose of sevelamer hydrochloride that can cause severe acidosis in 10% of patients was 3.5 g/day (95% confidence interval, 2.8–4.4). Table 2 indicates that sevelamer hydrochloride is commonly used at doses of 0.75–3.5 g/day in Japan. Another finding of the study was that in the absence of treatment with sevelamer hydrochloride, 4.5% of HD patients developed severe acidosis, whereas treatment with large doses of sevelamer hydrochloride was associated with the development of severe acidosis in 16% of patients. A similar trend was also noted in subgroup analysis based on sex and age. Considered together, the above results suggest that severe acidosis in HD

patients is probably related to the use of sevelamer hydrochloride.

The above correlation, however, does not imply causation. Multivariate analysis with appropriate correction for serum phosphate levels, dialysis dose (Kt/V), and dialysis duration are needed since certain confounders can impact acidosis. We could not perform such comprehensive analysis because of the lack of such raw data on individual patients, due to the fact that the Statistical Research Commission of the JSDT did not approve the supply of such data from the 2004 survey, because the term of public invitation for clinical research had already expired.

In our study, only a few CAPD patients developed severe acidosis. Pai and Shepler (17) commented that buffered dialysate solutions are continually exchanged on a more regular basis during peritoneal dialysis than during conventional HD, which may mitigate the risk of sevelamer hydrochloride-induced metabolic acidosis.

Sevelamer hydrochloride was introduced in Japan on 26 June 2003. Since then, the total usage of sevelamer hydrochloride in Japan has risen. Serum bicarbonate levels were measured in about 30% of patients in the 2004 survey (9), and in 25.7% of patients (59 581 patients out of 231 797) in a 2008 nationwide survey (18): both surveys were performed by the JSDT. But they did not research the relationship between bicarbonate level and the dose of sevelamer hydrochloride after the 2004 survey. This is the reason for using the 2004 survey in the present study. We speculate that serum bicarbonate levels are not measured in more than 70% of Japanese patients on HD who are treated with sevelamer hydrochloride, putting them at risk of an unrecognized state of acidosis.

Pharmaceutical companies that market sevelamer hydrochloride in Japan reported that the drug reduces serum bicarbonate in 1–5% of the patients. However, our results showed severe acidosis in 16.1% and moderate acidosis in 63.0% of patients treated with a high dose (≥ 5.25 g/day) of sevelamer hydrochloride.

What are the available countermeasures against sevelamer hydrochloride-induced acidosis? In our hospital, we reduced the dose of sevelamer hydrochloride, or stopped the use of this phosphate binder and/or prescribed sodium bicarbonate for patients with serum bicarbonate less than 16 mmol/L. In a study involving 33 patients treated with sevelamer hydrochloride, the dose was reduced or stopped in 14 patients (19), and acidosis improved in almost all patients after the dose change. In contrast, Akatsuka et al. (20) recommended the use of sevelamer hydrochloride in combination with calcium carbonate in HD patients because the latter has some buffering

effects and acts as a potent alkalizing agent. Furthermore, Sonikian et al. (21) corrected sevelamer hydrochloride-induced metabolic acidosis and hyperkalemia in HD patients by increasing dialysate bicarbonate concentration. Lindley et al. (22) corrected metabolic acidosis by switching sevelamer hydrochloride to lanthanum carbonate. Delmez et al. (10) performed a double-blind, randomized, crossover study to investigate the effects of sevelamer carbonate and sevelamer hydrochloride and reported a rise in bicarbonate level during treatment with sevelamer carbonate.

The above results call for careful monitoring of acidosis in HD patients treated with sevelamer hydrochloride. We recommend a reduction in the dose or withdrawal of sevelamer hydrochloride in those patients who show prognosis-threatening levels of acidosis. We speculate that the acidosis caused by sevelamer hydrochloride was not induced by chance, but was dependent on both the extent of metabolic acidosis before the administration of sevelamer hydrochloride and on the dose of sevelamer hydrochloride. We recommend measurement of serum bicarbonate level before administration of sevelamer hydrochloride, and routine monitoring during the treatment.

Limitations

The main limitation of this study is the lack of raw data for individual patients (e.g. serum phosphate, dialysis dose [Kt/V], and dialysis duration), and thus the inability to conduct multivariate analysis to exclude the effects of certain confounders. This was due to the rejection of our application to the Statistical Research Commission of the JSDT to the supply of such data from the 2004 survey. The rejection was due to the late submission of the application after the expiry date.

CONCLUSIONS

The percentage of patients on hemodialysis with severe acidosis increased significantly with increased dose of sevelamer hydrochloride. Severe acidosis is reported to affect prognosis of patients. We recommend measurement of serum bicarbonate level before administration of sevelamer hydrochloride, and to routinely repeat such measurement during the treatment.

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