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Effect of Continuous Administration of Conjugated Estrogen plus Medroxyprogesterone Acetate (Premelle®) in Postmenopausal Women in Taiwan

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Key Words
estrogen;
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Background. To compare the metabolic effects on lipids and acceptability and safety of, and compliance with, a continuous administration of conjugated estrogen plus medroxyprogesterone acetate (Premelle®) *versus* a placebo in non-hysterectomized postmenopausal women.

Methods. Sixty-six generally healthy, female, early post-menopausal women, from 45-60 years of age, were randomized for an administration of conjugated estrogen plus medroxyprogesterone acetate (Premelle®, Premarin 0.625 mg plus medroxyprogesterone acetate 2.5 mg/tablet orally) or a placebo for 6 months. The changes in each patient's lipid profiles from baseline, the frequency of hot flushes, bleeding occurrences, and climacteric symptoms, were evaluated. Safety was monitored by means of physical examination, Papanicolau smear, transvaginal ultrasonography, and laboratory check-up. Adverse events were also recorded.

Results. The difference before and after treatment in serum LDL-C and total cholesterol (TC) was statistically significant in the Premelle® group (LDL-C, $p = 0.006$, TC, $p = 0.040$). No statistically significant difference in the change from baseline was observed in the levels of LDL-C and TC in the placebo treatment group. There was a statistically significant change from baseline in menopausal symptoms, which were evaluated by the Greene Climacteric Scales in the Premelle® group. There was no clinically significant finding in the physical examination, vital signs, laboratory data, or endometrial thickness in either treatment group. The difference in the number of patients who reported an adverse event was not statistically significant between the 2 treatment groups.

Conclusions. This study demonstrated that Premelle® was effective in decreasing LDL-C and total cholesterol levels, and also showed an improvement in some menopausal symptoms, such as vasomotor and sexual dysfunction symptoms. No significant bleeding was observed with Premelle®, which was well tolerated in this study. The results of this study could support the use of Premelle® tablets as a convenient alternative hormone therapy.

Based on recent demographic data, a Taiwanese woman, like women in many other developed countries, can normally expect to live approximately 1 third (about 30 years) of her life span in a postmenopausal state.[1] Due to a chronic reduction of her estrogen secretions, such a state produces acute physical symptoms (e.g. hot flushes and incontinence) with attending psychological side effects (e.g. anxiety and depression), and leads to increased chronic risks of morbidity or mortality (e.g. bone fracture and coronary disease).[2] Three decades ago, medical research showed that estrogen therapy (ERT) provides short-term symptomatic relief and long-term survival benefits for postmenopausal women.[3]

In the early 1980's, the cyclic addition of progestins such as medroxyprogesterone acetate (MPA) to conjugated estrogen (CE) as a combination hormone therapy

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(HRT) regimen was found to drastically reduce the incidence rate of endometrial cancer without sacrificing the benefits of ERT alone.[3] However, this regimen significantly delayed the re-establishment of amenorrhea when compared to ERT alone.[4] This delay is often a primary reason for the > 70% non-compliance rate by American women who were prescribed cyclic HRT, despite the documented long-term cardio- and osteo-protective benefits.

In the last decade, comparative (continuous daily *vs.* cyclic HRT regimens) Premelle® (CE plus MPA) data from large randomized double-blinded US and European phase 3 clinical trials (≥ 1 year) showed a significant reduction in this delay using the continuous regimen,[4] while substantially maintaining the favorable lipid metabolism profile required for cardiovascular protection and the bone density increase needed for osteoporotic protection.[6,7] Although the initial incidence of irregular bleeding increased when compared to cyclic HRT, high (> 65%) compliance rates were observed in the women using a continuous regimen during this trial.

Patients receiving unopposed estrogen therapy have been reported to have an increased incidence of endometrial hyperplasia and an increased risk of endometrial adenocarcinoma.[8-11] Both can be reduced by the addition of a progestational agent to the replacement regimen.[12] However, the addition of progestins may diminish the beneficial effects of estrogen on the lipid profile, even though one study showed that the adding of progestin attenuates the beneficial effect of estrogen on plasma lipids in a dose-dependent manner.[12] Low-dose medroxyprogeterone acetate showed no statistically significant change in high dendity lipoportein cholesterol (HDL-C) concentrations.

A study of continuous estrogen/progestin therapy (combination of estrogen and progestin in a single tablet) *versus* cyclic estrogen/progestin therapy (addition of progestin to estrogen therapy from the 15 th to the 28 th day of the menstrual cycle) was done to evaluate the incidence of vaginal bleeding, endometrial histology, menopausal symptoms, blood pressure and serum lipid concentrations in menopausal women.[4,13,14] The study demonstrated that both treatments were equally effective in relieving the symptoms of atrophic vaginitis and hot flushes, and did not cause any significant change in blood pressure or HDL-C cholesterol concentrations. But vaginal bleeding was virtually eliminated in the group receiving continuous estrogen/progestin therapy.

This study was designed to compare the metabolic effects, acceptability, and safety of a continuous administration of conjugated estrogen plus MPA *versus* a placebo in non-hysterectomized postmenopausal women.

METHODS

Subjects

A group of 66 healthy postmenopausal women with intact uterus (45-60 years of age; mean: 53.3 ± 3.3 years) participated in the study. Menopause was diagnosed as a natural menopause of at least 6 months' duration, a follicle stimulating hormone level greater than 18 mIU/L, and a plasma estradiol level less than 30 pg/mL. No patients had previous history of liver disease, breast cancer, endometrial cancer, thrombophlebitis, thromboembolic disorders related to estrogen use, myocardial infarction or ischemic heart disease, chronic renal disease, cerebrovascular accident, uncontrolled hypertension, diabetes or metabolic bone disease, or had received any hormone treatment within one year previous. The following were not permitted during the study and would necessitate the withdrawal of the patient from the study: chronic use of steroids, fluoride, Vitamin D, rifampin, barbiturates, sulfonamide, and herbal medications, or the use of estrogen and progestins other than the study medications. The study was approved by the Institution Review Board (IRB), Taipei Veterans General Hospital, and written informed consent was obtained from all patients enrolled in the study.

Treatment

This was a double-blinded, single center, randomized, comparative outpatient study. Patients participated in a 7-day pre-study evaluation period followed by 6 treatment cycles (28 days per cycle). Enrollment was completed in 15 months. The entire study was approximately 21 months long. Sixty-six early postmenopausal women with 33 patients per study group were enrolled into this study. One group received 1 tablet of Premelle® (Premarin 0.625 mg and MPA 2.5 mg) orally daily for 28

days of each cycle. Another group took 1 placebo tablet daily for 28 days of each cycle. The treatment period was 6 cycles and the women were monitored following the 1st, 3rd, and 6th months.

Laboratory methods

During the 6-month treatment period, patients were asked to come in for a follow-up visit at 0 and 24 weeks after taking the medication, for laboratory determinations, including hematology, blood chemistry, lipid profiles and hormonal study, and transvaginal ultrasound. Blood samples were collected for laboratory tests. The lipid levels (total cholesterol [TC], HDL-C, low-density lipoprotein cholesterol [LDL-C] and triglycerides [TG]) were measured with an automatic analyzer (Hitachi-7600, Nakashi, Japan).

Clinical assessments

Each patient gave a complete medical history, including past medical history, surgical procedures especially related to reproductive and/or endocrine organs, and obstetrical history. The baseline visit was scheduled at least 7 days but not more than 21 days after the screening visit. Study visits were scheduled after the 1st, 3rd and 6th months. Menopausal symptoms were recorded by the patients using the Greene Climacteric Scale, and were then scored at each clinic visit.[15] The Greene climacteric scale is a brief but comprehensive and valid measure of climacteric symptomatology. Twenty-one menopausal symptoms fall into 4 main groupings: psychological (anxiety and depression subscales), somatic, vasomotor, and sexual dysfunction scales. Each scale was evaluated as follows: 0 = not at all, 1 = a little, 2 = quite a bit, and 3 = extremely. The following examinations were performed after completion of the 6- month treatment: complete physical examination, and adverse events. Study diary cards were maintained to record bleeding episodes and daily tablet intake on each calendar. Efficacy was evaluated as a comparison of changes in lipid profile, and frequency and severity of menopausal symptoms between the 2 treatment groups.

Statistical analysis

All measurements were listed and/or tabulated, and means and standard deviations, if appropriate, were calculated. Differences between the 2 groups were compared using either the paired and unpaired t-test, or ANOVA with baseline as covariate for continuous data, or by the Mantel-Haenszel method for categorical data.

All statistical tests were two-sided, and a p value of less than 0.05 was considered statistically significant.

RESULTS

Altogether, 66 patients were randomized into the 2 treatment groups, 33 patients in the Premelle® group and 33 patients in the placebo group. Fifty-one patients (26 in the Premelle® and 25 in the placebo group) completed the study. Table 1 presents the demographic and baseline features of the study groups. There was no statistically significant difference between the 2 treatment groups. A total of 51 patients were evaluated for patient compliance, since 15 patients did not return at visit 3. The difference was not statistically significant between the 2 treatment groups (Table 1). And, the difference in the mean number of missed tablets during the study period was not statistically significant between the 2 groups.

Lipid profiles

No statistically significant differences between the 2 treatment groups were observed in each item at baseline.

Table 1. Summary of patient demographics

Characteristics	Premelle® (n = 26)	Placebo (n = 25)	p
Age (years)	53.2 ± 3.1	53.3 ± 3.4	0.909
Age at menopause	49.8 ± 3.1	49.9 ± 3.4	0.940
YSM (months)	4.1 ± 0.9	4.0 ± 0.9	0.673
Weight (kgs)	56.0 ± 8.3	55.7 ± 6.6	0.851
Numbers of tablets missed	3.5 ± 4.6	6.0 ± 8.4	0.382

YSM = year since menopause; Values are means ± S.D.

As shown in Table 2, the levels of total cholesterol and LDL-C were reduced from baseline to a statistically significant degree in the Premelle® group (p = 0.040, 0.006 respectively), while the level of triglycerides decreased from baseline to a statistically significant degree in the placebo group (p = 0.008). The difference between the Premelle and placebo groups in the change from baseline on LDL-C and triglycerides was statistically significant. The difference in the lowering of the level of total cholesterol between the 2 treatment groups was in favor of the Premelle® group, and that of triglyceride in favor of placebo.

Climacteric symptoms

Table 3 shows the comparison of individual symptoms on the Greene Climacteric Scale between the 2 treatment groups. A statistically significant difference between the 2 groups was observed in the symptoms of loss of interest in sex after 24 weeks of treatment in favor of the Premelle® group. After 24 weeks of treatment, both treatment groups had statistically significant changes in the psychological, somatic and sexual dysfunction scales. In this study, loss of interest in sex was evaluated using the Greene Climacteric Scale. Although there was no statistically significant difference between the Premelle® and placebo groups in the sexual scale at baseline, the numbers of patients with severe loss of sexual interest decreased significantly after Premelle® treatment (24 weeks, p = 0.025) (Table 4).

Clinical assessment

There were no statistically significant changes from baseline in body weight, blood pressure, pulse rate, endometrial thickness, laboratory data, or the Pap smear between the 2 treatment groups. The data in Table 5 show that there were no statistically significant differ-

Table 2. Lipids profile during short-term treatment with placebo or Premelle® in early postmenopausal women

	Premelle®				Placebo				Premelle® *vs.* Placebo
Lipids	Baseline (mg/dL)	24 weeks (mg/dL)	Change (%)	p	Baseline (mg/dL)	24 weeks (mg/dL)	Change (%)	p	p
TC	208.6 ± 30.3	202.2 ± 29.7	-6.4 ± 17.1	0.040	214.2 ± 30.5	215.4 ± 35.7	1.2 ± 17.8	0.706	0.083
Triglyceride	107.8 ± 69.8	119.2 ± 69.5	9.4 ± 35.4	0.143	111.9 ± 49.5	96.9 ± 41.0	-15.0 ± 30.3	0.008	0.004
HDL-C	61.4 ± 15.0	62.9 ± 15.7	1.5 ± 8.7	0.323	61.3 ± 11.7	62.3 ± 11.5	1.0 ± 5.7	0.305	0.789
LDL-C	124.5 ± 24.5	112.7 ± 24.5	-11.8 ± 23.0	0.006	129.1 ± 33.3	130.2 ± 35.2	1.1 ± 20.0	0.763	0.018

TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Values are means ± S.D.
There were no statistical differences between the baseline of placebo and Premelle® groups.

Table 3. Effect of treatment on menopausal symptoms (Greene Climacteric Scale)

	Premelle®				Placebo				Premelle® vs. Placebo (24 wks)
	Baseline	24 weeks	Change (%)	p	Baseline	24 weeks	Change (%)	p	p
P (1-11)	4.8 ± 3.8	3.3 ± 3.0	-1.5 ± 3.4	0.017	4.6 ± 3.5	3.0 ± 2.6	-1.5 ± 3.4	0.015	0.764
A (1-6)	2.9 ± 2.5	2.1 ± 1.9	-0.8 ± 2.3	0.055	2.9 ± 2.4	1.8 ± 1.7	-1.1 ± 1.9	0.002	0.367
D (7-11)	1.9 ± 2.1	1.2 ± 1.4	-0.7 ± 1.9	0.043	1.6 ± 1.6	1.2 ± 1.4	-0.4 ± 1.7	0.200	0.674
S (12-18)	4.1 ± 3.3	3.0 ± 3.2	-1.1 ± 2.0	0.004	3.8 ± 3.3	2.6 ± 2.6	-1.2 ± 2.7	0.014	0.650
V (19-20)	1.3 ± 1.7	0.6 ± 1.1	-0.8 ± 1.5	0.005	1.0 ± 1.1	0.8 ± 1.1	-0.2 ± 1.1	0.256	0.116
Sex (21)	0.6 ± 0.8	0.3 ± 0.6	-0.4 ± 0.8	0.012	1.0 ± 0.9	0.6 ± 0.7	-0.4 ± 0.8	0.012	0.142
Total (1-21)	10.9 ± 7.0	7.0 ± 5.6	-3.8 ± 4.5	0.001	10.3 ± 6.8	7.0 ± 5.2	-3.3 ± 5.9	0.003	0.906

P = psychological scale; A = anxiety scale; D = depression scale; S = somatic scale; V= vasomotor Scale; Sex = sexual scale; values are means ± S.D.
Statistical analysis: paired and unpaired t-test.
There were no statistical differences between the baseline of placebo and Premelle® groups.

ences between the Premelle® and placebo groups with regard to the frequency of spotting and bleeding during each treatment cycle. There was a statistically significant change from baseline in the vasomotor scale in the Premelle® group after 24 weeks ($p = 0.005$) of treatment. No statistically significant change in the vasomotor scale was observed in the placebo group after 24 weeks ($p = 0.256$) of treatment.

Safety

There were 34 incidences of adverse events, 22 in the Premelle® group, and 12 in the placebo group. In the Premelle® group, the most frequent adverse events involved the respiratory system, digestive system, and special sense, followed by the nervous system. All adverse events were standardized using the CORSTART coding system (Table 6).

DISCUSSION

A protective effect on the cardiovascular system is strongly indicated in post-menopausal estrogen therapy. This beneficial effect is thought to result, in part, from changes in the lipid profile.[13,16] Because of the risk of uterine cancer, progestogen was introduced in combination with estrogen to modify the estrogen effect on the endometrium. Thereafter, questions arose as to whether progestin might negate the beneficial effects of estrogen on the lipid profile. Loba *et al*. evaluated the impact of adding MPA to continuous therapy with conjugated estrogen in postmenopausal women in a large randomized, double-blind clinical trial.[17] The results showed that serum LDL-C values decreased significantly ($p < 0.001$) from baseline in both the estrogen and estrogen plus MPA groups. The decrease in total cholesterol from

Table 4. Numbers of patients and severity of individual symptoms of loss of interest in sex

Visit weeks	Score	Premelle® (n = 33)	Placebo (n = 33)	*p* value of sex scale (Premelle® *vs* placebo)
Baseline	0	18 (55%)	11 (33%)	0.099
	1	9 (27%)	13 (39%)	
	2	6 (18%)	8 (24%)	
	3	0 (0%)	1 (3%)	
4th week	0	25 (76%)	21 (64%)	0.251
	1	7 (21%)	9 (27%)	
	2	1 (3%)	3 (9%)	
12th week	0	26 (79%)	19 (58%)	0.048
	1	6 (18%)	9 (27%)	
	2	1 (3%)	5 (15%)	
24th week	0	26 (79%)	17 (52%)	0.025
	1	5 (15%)	12 (36%)	
	2	2 (6%)	4 (12%)	

Statistical analysis: Mantel-Haenszel method.

Table 5. Mean frequency of spotting and bleeding regardless of severity between the Premelle® and Placebo Groups

	Spotting			Bleeding		
	Premelle® Mean ± S.D. (Range)	Placebo Mean ± S.D. (Range)	*p*	Premelle® Mean ± S.D. (Range)	Placebo Mean ± S.D. (Range)	*p*
Baseline	0.2 ± 0.9 (0-4)	0.3 ± 1.3 (0-7)	0.733	0	0	N.A.
1st month	0.6 ± 1.5 (0-6)	0.6 ± 2.5 (0-13)	0.995	0.2 ± 0.9 (0-5)	0.0 ± 0.2 (0-1)	0.337
2nd month	0.3 ± 1.3 (0-7)	0.2 ± 1.2 (0-7)	0.616	0.2 ± 1.2 (0-7)	0	0.321
3rd month	0.3 ± 1.1 (0-5)	0.3 ± 1.3 (0-7)	0.658	0.2 ± 1.2 (0-7)	0	0.260
4th month	0.2 ± 1.0 (0-5)	0.2 ± 1.2 (0-7)	0.626	0.0 ± 0.2 (0-1)	0	0.321
5th month	0.4 ± 1.3 (0-5)	0.2 ± 1.2 (0-7)	0.323	0.0 ± 0.2 (0-1)	0	0.321
6th month	0.2 ± 1.0 (0-5)	0.2 ± 1.2 (0-7)	0.626	0.0 ± 0.2 (0-1)	0	0.321

S.D. = standard deviation; baseline, unpaired t-test; Cycles 1-6, ANOVA F test; N.A. = not applicable.

Table 6. Numbers of incidences of adverse events using COSTART in the Premelle® and placebo groups

	Premelle®(n = 27)	Placebo (n = 25)
Body as a whole	0	2
Pain	0	1
Pain Abdomen	0	1
Digestive System	5	0
Gastritis	2	0
Pyorrhea	1	0
Rectal Disease	2	0
Edema	1	0
Musculoskeletal System	1	1
Arthrosis	1	1
Nervous System	4	4
Anxiety	0	1
Depression	0	1
Dizziness	2	1
Hypertension	0	1
Hypesthesia	2	0
Respiratory System	6	4
Bronchitis	1	1
Laryngitis	1	0
Pharyngitis	3	2
Sinusitis	1	1
Skin and Appendages	2	1
Eczema	1	0
Pruritus	0	1
Rash	1	0
Eye Disease	3	0

baseline in the estrogen and estrogen plus MPA groups was significant. However, the decrease in total cholesterol in the estrogen plus MPA group was significantly lower than that in the estrogen alone group. In the estrogen and estrogen plus MPA groups, HDL-C increased significantly. However, the increase in the HDL-C level in the estrogen plus MPA group was significantly lower than that in the estrogen group. For triglyceride levels, both the estrogen and estrogen plus MPA treatment groups had elevated values when compared to the baseline.

Our study comparing continuous combination therapy (Premelle®) with a placebo group showed that a statistically significant difference between the Premelle® and Placebo groups with regards to a LDL-C lowering effect ($p = 0.018$) was observed (Table 2). The Premelle® group demonstrated a statistically significant lowering effect on LDL-C and total cholesterol (LDL-C, -11.8 ± 23.0 mg/dL, $p = 0.006$, TC, -6.4 ± 17.1 mg/dL, $p = 0.040$), although the decrease in total cholesterol (6.4%) is less than other studies (10-13%).[17] No statistically significant changes in the level of LDL-C and total cholesterol (LDL-C, 1.1 ± 20.0 mg/dL, $p = 0.763$, TC, 1.2 ± 17.8 mg/dL, $p = 0.706$) were observed in the placebo group. There were no statistically significant changes that occurred in HDL from baseline in either group, although the level of HDL-C was elevated slightly (1.5 ± 8.7 mg/dL, $p = 0.323$ in the Premelle® group, 1.0 ± 5.7 mg/dL $p = 0.305$in the placebo group). The level of triglyceride showed a trend of increase (9.4 ± 35.4 mg/dL, p = 0.143) in the Premelle® group, which was similar to previous findings.[17] The level of triglyceride showed a trend of decrease (-15.0 ± 30.3 mg/dL, $p = 0.008$) in the control group, which was possibly due to small sample sizes. In general, the effect on the lipid profile was favorable in the Premelle® group, and the results were comparable to those in the previous study.

Menopause, in which a variety of endocrine, somatic and psychological changes occur because of an altered state of estrogen metabolism, is the most critical point in a woman's life. Estrogen therapy has been extensively utilized for the treatment of menopausal symptoms, including hot flushes and sweating at night. The vasomotor symptoms are usually relieved during the first cycle of treatment and may be relieved within days.[19] However, several studies have suggested that estrogen therapy has a causal relationship with the development of endometrial hyperplasia.[4,18-21] This led to the use of progestins to counteract the growth of the stimulating effect of estrogen on the endometrium.[20,22] To avoid the continued menstruation that usually accompanies the addition of sequential progestogen therapy, continuous combined estrogen and progesterone therapy has been commonly used as hormone therapy.

In this study, we used the Greene Climacteric Scale to evaluate menopausal symptoms. There was a statistically significant change from baseline in the vasomotor scale in the Premelle® group after 24 weeks ($p = 0.005$) of treatment. No statistically significant change in the vasomotor scale was observed in the placebo group after 24 weeks ($p = 0.256$) of treatment. Although there were no statistically significant differences between the Premelle® and placebo groups in relieving vasomotor symptoms, including hot flushes and sweating at night, the results were in favor

of the Premelle® group.

Another major problem related to estrogen deprivation is the symptomatology of urogenital atrophy. The vaginal wall becomes thin and the vaginal glands atrophic, leading to loss of lubrication and to dyspareunia.[23] The consequent reduction in sexual activity establishes a vicious cycle of a further loss of lubrication and worsening of atrophy. These changes are reversed, at least in part, by estrogen.[24] In this study, loss of interest in sex was evaluated using the Greene Climacteric Scale. The numbers of patients with severe loss of sexual interest decreased significantly after Premelle® treatment (24 weeks, $p = 0.025$) (Table 4).

Concerning the other menopausal symptoms, both treatment groups had statistically significant changes in the psychological scale, somatic scale, and depression scale from baseline and after treatment. The difference between the 2 treatment groups was not statistically significant. The reason for this minimal difference between the 2 groups could be the number of years from menopause. It has been postulated that menopausal symptoms tend to diminish 3 to 4 years after menopause in untreated women.

Our study used a placebo group as a control group in determining the effect of Premelle® on the bleeding pattern in postmenopausal women. Two patients in the Premelle® group and 3 patients in the placebo group of enrolled patients experienced spotting at baseline. Two patients in the Premelle® group and 1 in the placebo group reported spotting after 6 treatment cycles. There were no records of bleeding in either group at baseline. Only 2 patients reported slight bleeding during treatment in the Premelle® group. Statistically, the study showed that there were no significant differences between the Premelle® and placebo groups with regards to the frequency and severity of bleeding episodes.

Regarding safety concerns, our study demonstrated no significant differences in endometrial thickness (mm), adverse events, abnormal laboratory data, physical examinations, blood pressure, and pulse rates between the 2 treatment groups. None of the abnormal findings was clinically significant. Premelle® was well tolerated in this study.

Conjugated estrogen combined with MPA has been used in clinical practice to relieve menopausal symptoms in postmenopausal women for more than 50 years. The efficacy and safety of the combination have been well established in many clinical studies. Premelle® is combined conjugated estrogen and MPA in a single tablet. This study demonstrated that Premelle® was effective in decreasing the LDL-C and total cholesterol levels. The study also showed an improvement in some menopausal symptoms, such as vasomotor and sexual dysfunction symptoms. No significant bleeding was observed in the Premelle® group. Premelle® was well tolerated in this study. The results of this study support the notion that the Premelle® tablet is a convenient alternative hormone therapy.

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