

Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: Further exploration of "as needed" use

Elizabeth F. Juniper, MSc,^a Gordon H. Guyatt, MD,^{a, b} Brian Archer, MD,^c
Penelope J. Ferrie, BSc^a Hamilton, Ontario, Canada

Background: The objective of this study was to compare regular and "as required" (prn) use of aqueous beclomethasone dipropionate nasal spray (Beconase AQ nasal spray) in the treatment of ragweed pollen-induced rhinitis and to examine possible predictors of unsatisfactory symptom control in the group of patients who used it on a prn basis.

Methods: Sixty adults with ragweed pollen-induced rhinitis, who had participated in previous hay fever studies or who responded to media notices, were enrolled in the study. The study design was a randomized, unblinded, parallel group comparison between regular use (400 µg daily) and prn use of Beconase AQ spray during the 6 weeks of the ragweed pollen season. Patients recorded daily symptoms and medication use in diaries. The Rhinoconjunctivitis Quality of Life Questionnaire was administered, and patient satisfaction with symptom control was assessed at clinic visits.

Results: Symptoms and quality of life tended to be better in the regular group, but differences were not statistically significant. Twenty-seven percent of patients in the prn group reported unsatisfactory control of symptoms; they experienced significantly worse symptoms and quality of life than the remainder of the prn group and used significantly more Beconase. No obvious predictors of unsatisfactory control were identified. Patients who achieved satisfactory control in the prn group had symptom and quality of life scores that were very similar to those of the regular group.

Conclusions: Most patients can use Beconase AQ as needed successfully for the treatment of hay fever, but there may be an apparently unpredictable minority who do not achieve satisfactory symptom control or quality of life with this approach and who require regular treatment. (*J ALLERGY CLIN IMMUNOL* 1993;92:66-72.)

Key words: Hay fever, ragweed pollen, beclomethasone dipropionate, quality of life

If nasal steroid sprays are started before and used regularly throughout a pollen season, there is strong evidence from numerous studies that nasal symptoms can be very well controlled.¹⁻³ However, patients are often reluctant to take medications when they are free of symptoms, and

Abbreviation used
prn: "As needed"

physicians tend to prescribe "as needed" (prn) dosing with inhaled nasal steroids to avoid unnecessary use at times when pollen counts are low and when patients only experience mild allergic rhinitis.

In 1989 we carried out a randomized, double-blind parallel group trial to compare the effectiveness and side effects of regular versus prn use of beclomethasone dipropionate (Beconase AQ) nasal spray for the treatment of ragweed pollen-induced rhinitis.⁴ A double dummy technique was used to achieve blinding. This meant that all subjects used two nasal spray bottles, one regularly every morning and evening and the other only when needed. The results demonstrated that

From ^athe Department of Clinical Epidemiology, ^bthe Department of Medicine, and ^cthe Department of Radiology, McMaster University Medical Centre, Hamilton, Ontario, Canada.

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Reprint requests: Elizabeth F. Juniper, MCSP, MSc, Department of Clinical Epidemiology and Biostatistics, McMaster University Medical Centre, 1200 Main St. West, Hamilton, Ontario, Canada, L8N 3Z5.

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the patients who were using Beconase regularly experienced significantly less symptoms and enjoyed a better quality of life during the pollen season than those who only used the Beconase when needed. Although the study was methodologically sound in terms of avoiding expectation biases, the validity of the conclusions was questioned because some patients in the prn group may have underused the prn bottle because they were already using spray from the regular bottle (placebo) twice each day. The dosing choices made by the prn group may have been altered by the artificial environment of the blinded clinical trial, and the true difference between the two groups may have been overestimated.

We have repeated the study with the Beconase AQ nasal spray in unblinded fashion and have examined the characteristics of the patients in the prn group to determine whether it is possible to predict which patients will experience unsatisfactory symptom control.

METHODS

Subjects

Sixty adults (16 to 70 years of age) were recruited for the study from previous hay fever studies ($n = 58$) and from notices placed in the local media ($n = 2$). All subjects gave a history of rhinitis that required treatment during the last two ragweed pollen seasons, and all had a positive response to skin prick test with ragweed pollen extract. None were more than mildly sensitive to *Alternaria tenuis* or *Cladosporium* species, fungal spores that are in the air at the same time as ragweed pollen. No subjects had vasomotor or perennial rhinitis, chronic nasal obstruction, polyposis, or sinusitis. None had other illnesses that required administration of corticosteroids or serious illnesses that might have an impact on quality of life. Pregnant women and nursing mothers were excluded. No subject had used inhaled or orally administered steroids or astemizole for at least a month before starting the trial, and none had received allergen injection therapy within the last year. All participants signed an informed consent form that had been approved by the McMaster University Medical Center, Research Committee.

Study design

The study was an unblinded randomized comparison between two parallel treatment groups over a 6-week period. Subjects had duplicate skin prick tests with 10-fold serial dilutions of ragweed pollen extract (2.5 to 25,000 noon units) (Bencard Allergy Services, Weston, Ontario, Canada). Subjects who met the entry criteria were matched in pairs according to skin sensitivity to ragweed pollen extract, severity of hay fever the previous year, sensitivity to *A. tenuis* and *Cladosporium*

species, grass sensitivity, and gender. One of each pair was randomly allocated to take 2 puffs (100 μ g) of Beconase AQ nasal spray into each nostril every morning and every evening from Saturday August 10 (1 week before ragweed pollen was expected to be in the air) to Saturday September 21. If symptoms became troublesome, patients were instructed to increase the dose to 2 puffs per nostril four times per day (maximum daily dose, 800 μ g) until symptoms were controlled and then to reduce to 2 puffs twice a day. The other subject in each pair was instructed to start taking 1 puff of Beconase AQ nasal spray (50 μ g) into each nostril as soon as symptoms started and to use it every 4 hours up to four times per day (400 μ g) until symptoms were controlled and then to reduce the dose. If symptoms were troublesome, they were instructed to take 2 puffs at each application (maximum daily dose, 800 μ g). In both groups, subjects who were receiving the maximum daily dose of Beconase and who had troublesome nasal symptoms were instructed to use 60 mg terfenadine when needed, up to 120 mg daily.

Eye symptoms were treated with naphazoline eye drops, 1 drop per eye when needed, up to four times per day. If this was insufficient, sodium cromoglycate eye drops were added, 1 drop per eye four times per day. Asthma was treated with inhaled salbutamol, 200 μ g when needed, up to 800 μ g daily. If this was insufficient, beclomethasone dipropionate bronchial inhaler was added, up to 400 μ g daily. Subjects were instructed to contact the investigator if they experienced any problems and not to use any other medications for their hay fever.

Every morning and evening from August 10 to September 21, subjects recorded in a diary the severity (0 = nil, 1 = mild, 2 = moderate, 3 = severe) and duration (0 = nil, 1 = a few short episodes, 2 = frequent episodes, 3 = continuous) of sneezing, stuffy nose, runny nose, itchy nose, and eye symptoms. They also recorded at the end of each day the amount of trial medication, terfenadine, eye drops, and non-hay fever medications they had used during the previous 24 hours.

Subjects attended the clinic during the weeks of August 5 (before ragweed season), September 2 (mid-season), and September 21 (after ragweed season). At each visit, they completed the Rhinoconjunctivitis Quality of Life Questionnaire.⁵ At the same time their diary cards were checked for accuracy, medication use was reviewed, and side effects were documented. Beconase AQ bottles were weighed at each visit to ensure that patients in the regular group were taking the medication as instructed and that the patients in the prn group were scoring the amount used correctly in their diaries.

At the end of the study, patients were asked whether they were satisfied with the control of their nasal symptoms during the ragweed pollen season. The only responses allowed were yes and no.

Regular pollen counts were not available throughout

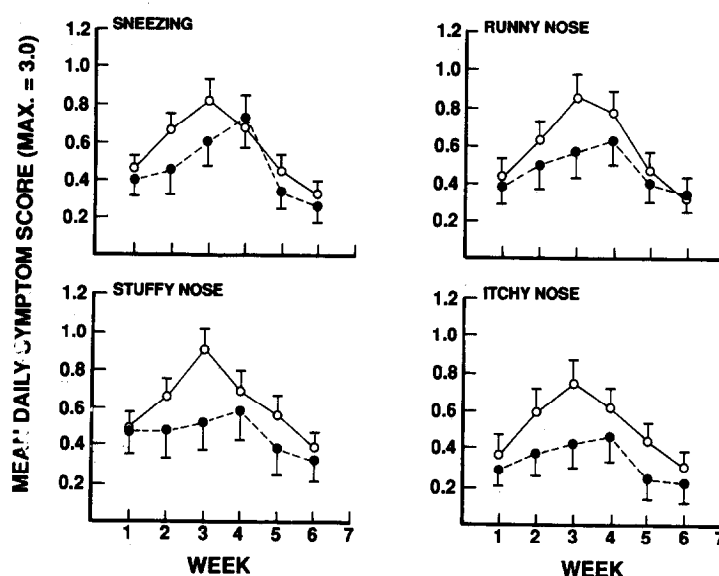


FIG. 1. Nasal symptoms in subjects using Beconase regularly (●—●) and prn (○—○). Probability of a treatment effect: sneezing $p = 0.19$, runny nose $p = 0.20$, stuffy nose $p = 0.16$, itchy nose $p = 0.09$. Error bars = SEM.

TABLE I. Patient characteristics

Characteristic	Regular treatment	PRN treatment
Number	30	30
Gender M/F	18/12	20/10
RW sensitivity		
Mean wheal diameter (mm)	3.65	3.64
SD	0.96	0.90
No. of subjects sensitive to fungal spores	9	7
No. of subjects sensitive to grass pollen	28	28
Severity of RW hay fever in 1990*		
Mild	9	10
Moderate	17	18
Severe	4	2

RW, Ragweed.

*Estimated from medication requirements and symptom severity.

this study, but a decade of regular observations in the Hamilton area has demonstrated that the ragweed pollen season is very consistent both in time and severity.^{6,7} Ragweed pollen first appears during the third week in August, reaches a peak during the last week in August, and becomes minimal by the third week in September.

Statistical analysis

Differences in symptoms, medication use, and quality of life between the two treatment groups were exam-

ined by means of a repeated measures analysis of variance with factors of treatment, time, and treatment-time interaction. Differences were considered significant at a p value of less than 0.05 (one-sided). Multiple regression analysis was used to examine predictors of satisfactory symptom control.

RESULTS

All 60 of the subjects, who were randomized equally between the two treatment groups, completed the study satisfactorily and were included in the analysis (Table I). The two patients who had not participated in the ragweed hay fever study the previous year (1990) were both randomized to the regular group.

In both treatment groups there was an increase in all nasal symptoms during the ragweed pollen season, but the increase was slight (maximum mean score <0.9 where 1.0 = mild), which indicates that on the whole symptom control in both groups was good (Fig. 1). Nevertheless, control in the regular group tended to be better than in the prn group for all nasal symptoms, but the majority of differences did not reach conventional statistical significance (treatment effect: sneezing $p = 0.19$, runny nose $p = 0.20$, stuffy nose $p = 0.16$, itchy nose $p = 0.09$; treatment-time interaction: sneezing $p = 0.08$, runny nose $p = 0.12$, stuffy nose $p = 0.028$, itchy nose $p = 0.18$). When just the 2 weeks at the height of the ragweed pollen season (weeks 3 and 4) were analyzed alone, the

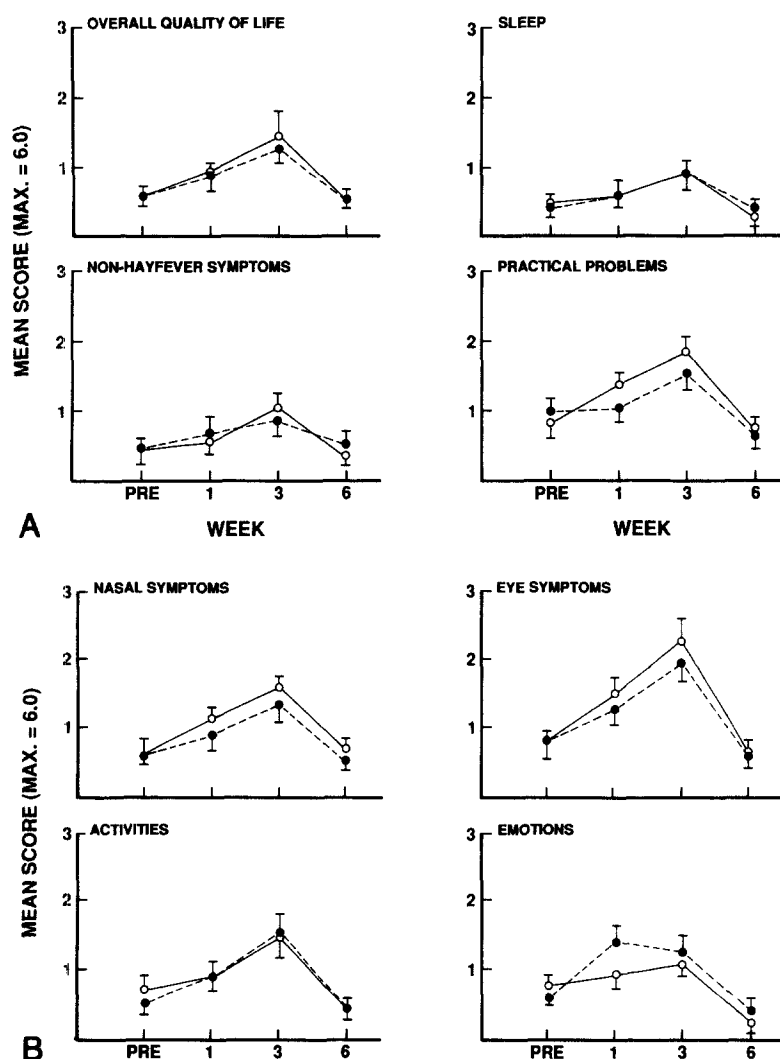


FIG. 2. Quality of life in subjects using Beconase regularly (●---●) and prn (○—○). **A.** Probability of a treatment effect: overall quality of life $p = 0.25$, sleep $p = 0.33$, non-hay fever symptoms $p = 0.37$, practical problems $p = 0.20$. **B.** Probability of a treatment effect: nasal symptoms $p = 0.06$, eye symptoms $p = 0.34$, activities $p = 0.30$, emotions $p = 0.50$. Error bars = SEM.

data still failed to show a significant treatment effect (sneezing $p = 0.29$, runny nose $p = 0.11$, stuffy nose $p = 0.08$, itchy nose $p = 0.08$). A similar pattern and statistical outcome was observed for all domains of quality of life (Fig. 2).

The use of terfenadine for uncontrolled nasal symptoms was similar in the two treatment groups ($p = 0.32$) (Fig. 3). Similarly, there was no evidence of any difference in eye symptoms ($p = 0.83$) or eye drop use ($p = 0.43$) between the two treatment groups (Fig. 3).

At the end of the study, eight of the 30 subjects in the prn group and one of the 30 subjects in the regular group reported that they did not achieve satisfactory control of their symptoms during the

pollen season ($p = 0.02$) (Table II). This difference between regular and prn treatment supports the trend observed in the diaries and the quality of life assessment.

Nasal symptoms in the eight dissatisfied patients in the prn group have been compared with those in the 22 satisfied patients in the same group (Fig. 4). The greatest differences were for itchy nose and sneezing and were significant ($p = 0.001$ and $p = 0.03$, respectively). The differences could not be attributed to Beconase use (dissatisfied patients: 3.14 puffs/nostril/day, satisfied patients: 2.35 puffs/nostril/day). No obvious clinical characteristics (sensitivity to ragweed, fungal spores, and grass pollen; severity of ragweed

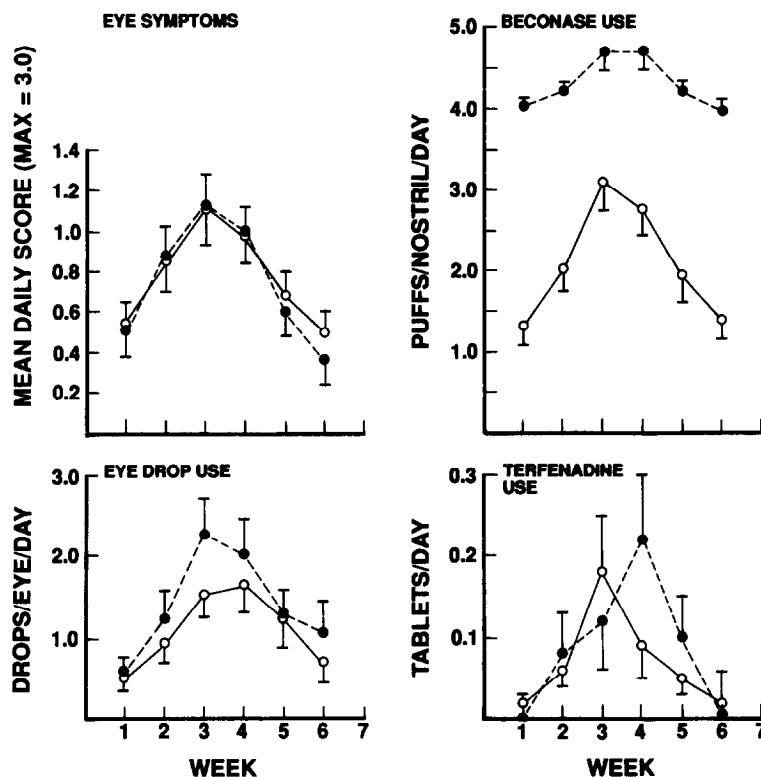


FIG. 3. Eye symptoms, eye drop use, Beconase use, and terfenadine use in patients using Beconase regularly (●—●) and prn (○—○). Probability of a treatment effect: eye symptoms $p = 0.83$, eye drop use $p = 0.43$, Beconase use $p = 0.0001$, terfenadine use $p = 0.32$. Error bars = SEM.

TABLE II. Characteristics of patients in the PRN group

Characteristic	Good control	Poor control
Number	22	8
Gender M/F	17/5	3/5
RW sensitivity		
Mean wheal diameter (mm)	3.55	3.79
SD	0.97	0.53
Subjects sensitive to fungal spores (%)	18.2	26.7
Subjects sensitive to grass pollen (%)	90.9	100.0
Control of RW hay fever symptoms in 1990		
Excellent	11	3
Very good	11	4
Fair	0	1
Severity of RW hay fever in 1990		
Mild	7	3
Moderate	13	5
Severe	2	0
Amount of Beconase AQ used in 1990 (gm)	23.74	28.25
SD	15.6	10.6

RW, Ragweed.

hay fever in 1990, and Beconase use and success for ragweed hay fever control in 1990⁸), could discriminate between the satisfied and dissatisfied patients in the prn group. However, in the dissatisfied patients all nasal symptoms were already more severe during the initial treatment week of the study (Fig. 4). Nasal symptoms in the satisfied patients in the prn group were very similar to those experienced by the patients in the regular group (Fig. 4).

DISCUSSION

The data from this unblinded study showed a trend suggesting that Beconase AQ nasal spray might have slightly better efficacy when it is used regularly than when it is used only when needed. However, the differences between the two dosing methods did not reach statistical significance, which suggests that this difference may have occurred by chance alone.

The statistical results of this unblinded comparison are different from those of the blinded study in which regular treatment was found to be significantly better than prn use.⁴ However, a review of the data suggests that the clinical interpretation for both studies is probably very similar. In

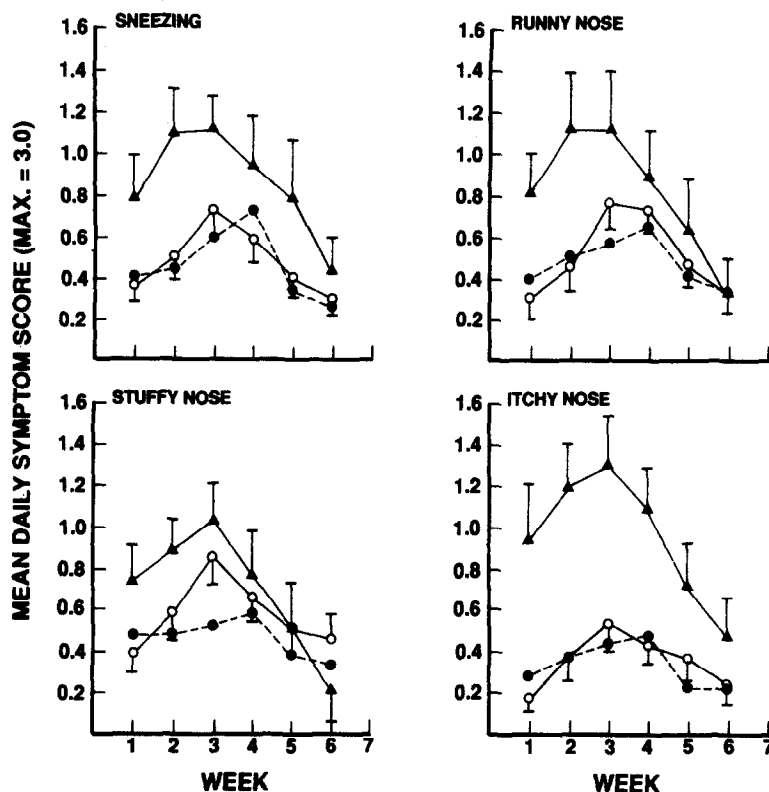


FIG. 4. Nasal symptoms in patients in the prn treatment group reporting unsatisfactory (▲—▲) and satisfactory (○—○) symptom control compared with patients using regular Beconase (●—●). Probability of a difference between the satisfied and dissatisfied patients: sneezing $p = 0.03$, runny nose $p = 0.10$, stuffy nose $p = 0.56$, itchy nose $p = 0.001$. Error bars = SEM (for satisfied and dissatisfied patients in the prn group only).

both studies both regular and prn treatment were associated with low symptom scores (maximum mean score <0.9 where $1.0 =$ mild) and minimal impairment of quality of life, which suggests that efficacy is good with both dosing regimens. In both studies the actual differences between regular and prn use were similar, small, and probably clinically unimportant.

Why were the differences between the two treatment groups statistically significant in one study and not the other? The simplest explanation is that there was insufficient power in the unblinded study in which the variance, for some unknown reason, was slightly larger. However, the differences between the two studies may have occurred for other reasons. In the blinded study the mean number of applications of Beconase per day in the prn group at the height of the season was 2.09, whereas in the unblinded study it was 3.12 applications per day. This suggests that either the ragweed pollen season was more severe during the unblinded study or that the study procedures may have affected prn use. In the blinded study the patients were already taking 2 puffs of nasal spray (placebo) every morning and evening, and this may have inhibited them from using the

prn canister more frequently. Thus in keeping with the original criticism of the blinded study, the artificial blinding procedure may have exaggerated the difference between the two groups. Conversely, in the unblinded study the prn group may have tended to use their nasal spray more frequently because they knew they had been randomized to the regimen that might be less effective. However, as already discussed, whatever the explanation for the statistical difference between the studies, the actual difference between regular and prn use in both studies was so small that it is unlikely to be of clinical significance (Figs. 1 and 2).

Eight patients in the prn group reported that they did not achieve satisfactory control of their symptoms compared with only one patient in the regular group. These results need to be interpreted with caution because the study was unblinded and the subjective assessment may have been biased by conversations during the study. If one accepts this limitation, the results may be worthy of further exploration because the data of the eight dissatisfied patients appear to account for most of the differences observed between prn and regular treatment. If there is a distinct subgroup, it would be useful to be able to identify them

so that they may be advised to use regular prophylactic treatment. In this study all of the likely clinical variables (e.g., ragweed sensitivity and hay fever severity) were not good predictors of symptom control. However, the results do suggest avenues worthy of further exploration. First, nasal irritation (nasal itching and sneezing) was the most troublesome nasal symptom in the dissatisfied group, suggesting a possible difference in the mucosal response to either the pollen or the inhaled steroid. Second, these patients recorded more severe symptoms during the first week of the study despite similar sensitivities to fungal spores and grass pollen and no evidence of perennial rhinitis. Third, in interviews with the patients at the end of the study, most reported that severe symptoms developed very rapidly and that they found themselves trying to play catch-up at a time when pollen counts were rising. Further studies are needed to confirm the presence of this distinct group of patients, to evaluate ways of identifying them, and to investigate possible pathologic differences.

The clinical implications of this study are that most patients with seasonal allergic rhinitis can achieve satisfactory symptom control and quality of life using a prn Beconase AQ regimen, such as that used in this study. If satisfactory control is not achieved by this approach, patients should be changed to a prophylactic, regular regimen.

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