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Side Effects of Minocycline: Different Dosage Regimens

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The incidence of side effects due to two dosage regimens of minocycline was examined over a 5-day period. A total of 60 normal women volunteers were randomly assigned in a double-blind manner to either a group who took 100 mg of minocycline twice a day or a group who took 75 mg of minocycline twice a day for 5 days. Both groups were comparable from the standpoints of age, size, race, and the use of oral contraception, nicotine, and ethanol. They were seen on a daily basis, and symptoms were evaluated by both volunteers (from diaries) and physicians. Minocycline serum concentrations were determined on blood samples taken 2 h after the a.m. dose. Volunteers taking 150 mg of minocycline per day had significantly lower serum antibiotic concentrations than those taking 200 mg per day. However, both low- and high-dose groups exhibited similar incidence and prevalence of recorded symptoms, with the single exception of nausea, where the low-dose group had fewer symptoms than the high-dose group ($P = 0.035$). Symptomatic volunteers did not have higher serum concentrations of minocycline than their asymptomatic counterparts. When either weight or surface area was examined with antibiotic serum concentration there was a significant inverse correlation between the two on day 2 for both groups and also on day 4 for the low-dose group. It is concluded that, in women, a dose of 150 mg of minocycline per day is associated with the same degree of side effects as a dose of 200 mg per day.

Two recent and extensive reviews (1, 3) of minocycline have summarized much of the literature concerning the occurrence of vestibular dysfunction related to this antimicrobial. Both stressed the need for more objective evaluation of this problem. By administering 200 mg of minocycline per day in a double-blind manner, a previous study of ours showed that vestibular and other side effects in women were far more prevalent in individuals taking the antimicrobial than in those taking a placebo (4). However, in men only loss of balance was significantly increased by the drug. Since the women in that study were significantly smaller than the men and because they also had significantly higher blood levels, it was thought that the increased incidence of side effects in the women might be related to higher minocycline serum concentrations. For this reason it was decided to study two different dosage regimens in women to determine whether 150 mg of minocycline per day would result in a significant decrease in the incidence of side effects as contrasted with 200 mg per day. The other aim of this study was to obtain daily peak minocycline serum concentrations from all volunteers and to relate these concentrations with the occurrence of side effects and also the size of the volunteers as measured by weight and body surface area.

MATERIALS AND METHODS

Volunteers. A total of 60 healthy volunteers were selected after history, physical examination, white blood count, differential, hematocrit, urinalysis, and a negative pregnancy test were taken. The volunteers consisted of students and university and hospital employees. Hematological tests and urinalyses were repeated on the third and fifth days of minocycline ingestion. Persons allergic to tetracycline, those taking antacids, or those who had a past history of vertigo or lightheadedness were excluded from the study. A full-disclosure consent form outlining all the possible side effects of the drug was signed by each volunteer. The study protocol and consent forms were reviewed and approved by the University of Vermont Human Experimentation Committee to conform to the National Institutes of Health guidelines.

Volunteers were randomly assigned into one of two equal-size groups in a double-blind fashion. One group was to receive 100 mg of minocycline twice a day for five days and the other group was to receive 75 mg twice a day for the same duration of time. No differences were observed between the characteristics of the two groups (Table 1). Volun-

TABLE 1. *Characteristics of the volunteers*

Variable	Group	
	Low dose	High dose
Minocycline dose/day (mg)	150	200
No. of volunteers	30	30
Mean age (yrs)	26.9 ± 1.4[a] (20–52)[b]	25.4 ± 0.91 (18–41)
Mean weight (pounds [kg])	132.6 ± 3.0 (60.2 ± 1.4) (100–180 [45.4–81.7])	133.1 ± 3.7 (60.4 ± 1.7) (108–180 [49.0–81.7])
Mean height (inches [cm])	63.9 ± 0.7 (163.9 ± 1.8) (51–70 [130.8–179.5])	66.0 ± 1.3 (169.2 ± 3.3) (55–71 [141.0–182.1])
Race		
Caucasion	30 (100)[c]	27 (90)
Other		3 (10)
Oral contraception	5 (17)	7 (23)
Smoker	7 (23)	7 (23)
Uses ethanol	25 (83)	26 (87)
Regular exerciser	16 (53)	19 (63)

[a] Standard error of the mean.
[b] Range.
[c] Percent.

teers were given one capsule in the morning upon arrival at the Clinical Research Center at the University of Vermont and a remaining pill to take in the evening, 12 h later. No directions were given as to when food might be ingested in relation to taking the minocycline since fat (2) or milk (3) minimally affect absorption of the drug.

Volunteers were seen each morning when they came to the Clinical Research Center to take the minocycline, and side effects were evaluated at that time. Volunteers presented a diary of any symptoms observed during the preceding 24 h and were also queried by one of the authors concerning side effects. Used medication vials were turned in each day from the previous day and the volunteers were given a new recording sheet. The diary sheets divided the day in six hourly intervals, and side effects were scored for both duration and severity status as follows—duration: (i) symptoms lasting less than 2 min; (ii) symptoms lasting from 2 min to 1 h; (iii) symptoms lasting from 1 to 6 h; (iv) symptoms lasting for more than 6 h; and severity: (i) minimal, noticeable symptoms but no limitation of daily activity; (ii) slight limitation of daily activity; (iii) definite limitation of daily activity but still active; (iv) limitation of activity to bed or chair.

Bioassay. Venous blood was obtained from each volunteer approximately 2 h after the a.m. dose. This time was felt to approximate most nearly the peak serum concentrations of the antimicrobial from previous studies (2). Bioassay for serum minocycline concentrations was done by a standard agar diffusion assay by using *Bacillus subtilis* spores, ATCC 6633 (6).

RESULTS

Major symptoms that occurred in both groups of volunteers were lightheadedness and a feeling of disassociation (a "spaced out" feeling; Table 2). There were no symptoms in the group taking 150 mg per day that were significantly less prevalent than in those taking 200 mg per day other than nausea, which occurred in 23.3% of the former group and 50% of the latter group ($P = 0.035$). Vestibular symptoms, which represented a combination of dizziness, loss of balance, lightheadedness, and tinnitus, were

TABLE 2. *Incidence of side effects*

Symptom	No. of patients experiencing side effects from:	
	150 mg/day (total = 30)	200 mg/day (total = 30)
Lightheadedness	16 (53.3)[a]	16 (53.3)
Disassociation ("spaced out")	15 (50.0)	14 (46.7)
Headache	12 (40.0)	10 (33.3)
Difficulty concentrating	11 (36.7)	13 (43.3)
Dizziness (vertigo)	7 (23.3)	10 (33.3)
Loss of balance	7 (23.3)	8 (26.7)
Nausea	7 (23.3)	15 (50.0)
Weakness	7 (23.3)	7 (23.3)
Euphoria	4 (13.3)	3 (10.0)
Tinnitus	3 (10.0)	3 (10.0)
Rash	3 (10.0)	1 (3.3)
Visual problems	3 (10.0)	1 (3.3)
Diarrhea	3 (10.0)	0 (0.0)
Vomiting	2 (6.7)	2 (6.7)
Other[b]	14 (46.7)	12 (40.0)
Vestibular	16 (53.3)	20 (66.7)
All symptoms	25 (83.3)	23 (76.7)

[a] Numbers in parentheses indicate percentages.
[b] Includes a wide variety of complaints. Included in the low-dose group were fatigue, constipation, sweating, palpitations, insomnia, delayed menses, tremor, edema around the eyes, and tingling of face. Included in the high-dose group were heartburn, backache, insomnia, irritability, depression, dyspepsia, edema around the eyes, constipation, and fatigue.

present in 53.3% of the individuals taking the lower dose of minocycline and were not significantly less frequent (66.7%) in volunteers taking the higher dose. When all symptoms were considered, individuals on the low-dose regimen had an increased rate of side effects (83.3%) from those on the high-dose regimen (76.7%). In either of the two groups, the peak number of individuals experiencing either vestibular or any symptoms was on day 2, and there appeared to be a slight reduction in the number of individuals experiencing symptoms after day 2. Moreover, symptomatic individuals in the low-dose group did not have either lessened duration or severity of symptoms when compared with similar individuals in the high-dose group.

Only one volunteer, a subject in the low-dose group, was unable to complete the study. After taking minocycline on the morning of the third day of the study, she declined to continue because she did not like the feeling of disassociation. However, she only considered this symptom to be of severity grade 1 even though it was of >6 h in duration each day. She also noted headache and lightheadedness of similar severity and duration. There were two volunteers in the high-dose group who omitted the 10th or last dose of minocycline, but this was an oversight and not because of symptoms.

Table 3 shows the minocycline serum concentrations for both of the groups. It is evident that the women taking 200 mg of minocycline per day had significantly higher serum minocycline concentrations on each day compared with those on the lower dosage regimen. It is also apparent that those individuals taking 200 mg a day had a mean serum concentration that was highest on day 5, whereas those taking 150 mg per day peaked on day 4. Also shown is that there was considerable variation in the minocycline serum concentrations that were achieved in these volunteers.

An analysis of the relationship of minocycline serum concentrations and individuals with vestibular symptoms is shown in Table 4 for both the low- and high-dose groups. This table only considers vestibular symptoms, but analyses considering other symptoms revealed similar findings. There is no indication that symptomatic volunteers have higher levels of minocycline than those with no symptoms.

The relationship between minocycline serum concentration and body surface area was analyzed for each study day in both groups of volunteers. In this analysis the minocycline serum concentrations were analyzed versus body surface area, but similar findings were true when this analysis utilized weight. There was a significant inverse correlation between serum concentrations and body surface area for both groups on day 2 ($P = 0.02$, Pearson's correlation coefficient). A significant

TABLE 3. *Minocycline serum concentrations in volunteers*

Study day	Serum concn (μg/ml ± standard error of the mean) at:		P^a value
	150 mg/day	200 mg/day	
1	1.3 ± 0.08 (0.6–2.2)[c]	1.7 ± 0.15[b] (<0.5–3.5)	<0.01
2	2.9 ± 0.14 (1.3–4.6)	3.5 ± 0.20 (1.8–6.0)	0.02
3	2.7 ± 0.14 (1.2–4.4)	3.8 ± 0.15 (2.5–6.0)	<0.001
4	3.1 ± 0.19 (1.5–5.6)	3.9 ± 0.19[d] (2.3–6.0)	<0.01
5	3.0 ± 0.20 (1.2–5.7)	4.1 ± 0.22[d] (2.0–7.1)	<0.001

[a] *P* value derived from an analysis of variance.
[b] Two volunteers in this group had serum concentrations on this day of <0.5 μg/ml. A value of 0.5 μg/ml was assigned to these two values to calculate this mean.
[c] Numbers in parentheses signify range.
[d] These values were calculated on the basis of 29 volunteers, since one volunteer dropped out of the study after day 3.

TABLE 4. *Relationship between mean minocycline serum concentrations on each study day for volunteers with and without vestibular symptoms*

Study day	150 mg of minocycline/day				200 mg of minocycline/day			
	No. with symptoms	Serum concn (μg/ml)	No. without symptoms	Serum concn (μg/ml)	No. with symptoms	Serum concn (μg/ml)	No. without symptoms	Serum concn (μg/ml)
1	4	1.55 ± 0.36[a]	26	1.21 ± 0.07	5	1.24 ± 0.34	25	1.81 ± 0.16
2	12	2.63 ± 0.24	18	2.99 ± 0.17	14	3.88 ± 0.34	16	3.13 ± 0.18
3	12	2.70 ± 0.19	18	2.62 ± 0.20	13	3.96 ± 0.23	17	3.64 ± 0.19
4	10	3.16 ± 0.37	19	3.04 ± 0.22	9	4.37 ± 0.45	21	3.70 ± 0.19
5	9	2.92 ± 0.46	20	3.03 ± 0.21	12	4.02 ± 0.38	18	4.21 ± 0.28

[a] Values ± standard error of the mean.

correlation was also present on day 4 in the low-dose group ($P = 0.01$). Despite their significance, the magnitude of these correlation coefficients was not large—they ranged from -0.395 to -0.449. In addition, examination of symptoms and body size revealed no significant relationship between these two parameters. Furthermore, analysis of factors such as use of oral contraceptive pills, smoking, use of ethanol, and whether one was a regular exerciser did not have any relationship to the occurrence of symptoms.

Hematological values and urinalyses were unaffected by minocycline in both groups, and no relationship between hematocrit and symptoms could be demonstrated.

DISCUSSION

When compared, the types and incidence of side effects that we observed in these two groups of volunteers taking either 150 or 200 mg of minocycline per day were quite similar to those of the group of 27 women taking 200 mg of minocycline per day in our previous study (4). The incidence of vestibular symptoms in women in the previous study was 70.4% in contrast to the incidence of 66.7% that we observed in the current study. The similarity in incidence of side effects occurring in the two studies would seem to indicate the validity of the incidence of side effects observed in the current study despite the fact that it did not contain a placebo group. As in our previous study, we also observed that the peak incidence of side effects was on the second day of drug ingestion.

One symptom that was not recorded in the previous study was that of disassociation ("spaced out" feeling), which was quite prevalent in the current study. It is probable that this symptom was not described as disassociation in the previous study and probably was considered to represent lightheadedness or difficulty in concentrating. Nonetheless, in the current study this side effect was noted to be quite prevalent and also very distressing to the volunteers.

Other than nausea, which was significantly less prevalent in the low-dose group of volunteers, all other symptoms were as prevalent in those individuals taking 150 mg of minocycline per day as with the group taking 200 mg per day. This finding was somewhat surprising since it was felt that, if minocycline serum concentrations could be significantly reduced, then side effects might also be reduced. Clearly this hypothesis was not verified. By reducing the dose of minocycline, it was impossible to reduce significantly the incidence of side effects other than nausea, and when the duration or severity of various symptoms was compared for symptomatic individuals in the two groups, no significant difference between them was noted.

It is not surprising that serum concentrations could not be correlated with the occurrence of symptoms since symptoms generally could not be decreased by reducing the dose of minocycline and, in turn, significantly reducing serum concentrations. On the other hand, data on serum concentrations of the antimicrobial were limited to a single determination each day. Hence, it might have been possible to demonstrate a significant correlation between serum concentrations and symptoms if more complete data were available concerning serum concentrations. It should be noted, however, that there was also no correlation between body size and symptoms, and this comparison should not suffer from any deficiency in available data. It is also possible that the symptoms of minocycline toxicity are related to concentrations of the drug in the central nervous system and do not reflect blood concentrations. Good diffusion of minocycline into cerebrospinal fluid has been reported (5). It would be interesting to see how cerebrospinal fluid concentrations of minocycline would correlate with the occurrence of symptoms.

Correlation of minocycline serum concentrations and the size (body surface area) of the volunteers revealed that there was a significant inverse relationship between the two in both low- and high-dose groups only on day 2 and this was only at a level of around -0.4 (Pearson's r value). Why this should have occurred only on day 2 is puzzling, but it may indicate that certain body compartments become saturated with drug over several days and, after this occurs, there no longer is a significant inverse relationship present between body size and minocycline serum concentrations. However, on day 4 in the low-dose group such a significant relationship was also present. Again the relationship between minocycline blood concentrations and body size may be somewhat muted because we have only obtained single 2-h blood samples, which certainly do not represent peak drug concentrations for some volunteers. Bernard et al. (2) were not able to show any relationship between body surface area and peak minocycline concentrations, but their analysis was based on concentrations after a single dose of drug.

This study does not allow us to determine why minocycline causes symptoms primarily in women, but not men, taking this drug. It is

noteworthy that the women taking 150 mg of minocycline per day in this study had approximately the same serum concentrations of minocycline as the men taking 200 mg of minocycline in the previous study. Others have also noted that women have higher serum concentrations of minocycline than men when receiving equal doses (2). Yet, the women taking 150 mg of minocycline per day had an incidence of side effects which considerably exceeded those noted in the men taking 200 mg of minocycline per day, though such a retrospective comparison may not be entirely valid. Thus, vestibular symptoms occurred in 53.3% of the women in the present study, whereas they occurred in 27.8% of the men. It therefore appears as if women have an increased tendency for vestibular and other symptomatology related to the ingestion of minocycline, which may possibly be related to intrinsic differences in women such as estrogens. However, there was no augmentation of symptoms in those individuals taking oral contraceptives. Studies of the incidence of side effects in postmenopausal women as contrasted with premenopausal women might shed some light on the possible synergistic toxicity of estrogens and this antimicrobial.

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