ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1977, p. 712-717

Vol. 11, No. 4
Printed in U.S.A.

# Side Effects of Minocycline: A Double-Blind Study

W. LEE FANNING,[1] DIETER W. GUMP,* AND ROBERT A. SOFFERMAN

*Department of Medicine, Division of Infectious Diseases*, and the Department of Surgery, Division of Otolaryngology, University of Vermont College of Medicine, Burlington, Vermont 05401*

Received for publication 19 October 1976

We studied the incidence and type of side effects of minocycline in a double-blind study. A total of 45 volunteers (18 men and 27 women) were given minocycline, and 44 volunteers (23 men and 21 women) were given placebo. The men in both the minocycline and placebo groups were significantly ($P < 0.0001$) larger than the women in the comparable groups. Minocycline dosage was 100 mg every 12 h for 5 days, and placebo was administered in an identical manner. Minocycline serum concentrations were determined in 12 volunteers at 1, 2, 4, and 6 h after the morning doses on days 1, 3, and 5 of the study. Side effects were recorded by volunteers in diaries and also through daily interviews and were evaluated by examination and electronystagmography. Peak minocycline serum concentrations were seen by day 3 and correlated with the peak onset of side effects. These concentrations were significantly higher in women than in men. Vestibular side effects occurred in 70.4% of the women on minocycline and significantly ($P < 0.0001$) exceeded the rate of the women on placebo (9.5%). Only loss of balance was significantly ($P < 0.05$) increased in the men taking minocycline as contrasted with men on placebo. Electronystagmography generally revealed no abnormalities. Side effects were usually not severe: four volunteers in the minocycline group and two in the placebo group discontinued their capsules because of side effects. It is concluded that women experience an unacceptably high incidence of side effects from minocycline, and this may be related to their higher serum concentrations, which in turn may relate to their smaller size.

Minocycline has been shown to be an effective drug for meningococcal prophylaxis (8). Many recent reports, however, have indicated a high incidence of side effects from minocycline (3, 6, 10, 15), and the Center for Disease Control now recommends rifampin for meningococcal prophylaxis (4). Recent studies showing a high incidence of side effects were, however, retrospective and not double blind. Therefore, this double-blind study was undertaken to document the frequency and character of side effects associated with minocycline.

## MATERIALS AND METHODS

**Volunteers.** A total of 89 healthy volunteers were selected after history, physical examination, white blood count, differential, hematocrit, urinalysis, and a negative pregnancy test. The volunteers consisted of students and university and hospital employees. Hematological tests and urinalyses were repeated at the conclusion of the study. Persons allergic to tetracycline, those taking antacids, or those who had a past history of vertigo or light-headedness 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.

Volunteers were randomly assigned into the placebo or the minocycline group in a double-blind fashion. The study utilized the out-patient facilities of the Clinical Research Center at the University of Vermont. The medications were supplied in identical packets for each volunteer indicating the order in which each capsule would be taken over the course of 5 days. The 45 volunteers in the minocycline group received 100-mg capsules at 8:00 a.m. and 8:00 p.m. for 5 consecutive days, and the 44 volunteers in the placebo group received placebo capsules in a similar manner.

Volunteers were seen once a day to evaluate side effects, but it was up to the volunteer to mention any problems, and only then were further questions asked concerning the complaint and related side effects. Used medication packets were turned in each day from the previous day. Volunteers were given recording sheets that divided the day into six hourly intervals to record the onset of side effects while at home. Side effects were scored for both duration and severity each day 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

[1] Present address: 100 Wendell Ave., Pittsfield, MA 01201.

severity: (i) minimal, noticeable symptom, but no limitation of daily activity; (ii) mild, slight limitation of daily activity; (iii) moderate, definite limitation of daily activity, but still active; (iv) severe, limitation of activity to bed or chair.

The mean age of both the minocycline and placebo groups was 27 years, and ages ranged from 19 to 52 years in the minocycline group and from 18 to 52 years in the placebo group. There were 48 women and 41 men overall with 27 women and 18 men in the minocycline group and 21 women and 23 men in the placebo group. The mean surface area in the placebo group was 1.97 $m^2$ for the men and 1.63 $m^2$ for the women and, in the minocycline group, 1.89 $m^2$ for the men and 1.61 $m^2$ for the women. The difference in surface area between men and women in both groups was significant ($P < 0.0001$, Student's $t$ test).

**Bioassay.** Twenty volunteers (twelve minocycline and eight placebo) had blood drawn at 1, 2, 4, and 6 h after the 8:00 a.m. capsule on days 1, 3, and 5 to determine concentrations of minocycline in their serum. Urine assays were done on the morning of day 5 at 7:30 a.m. for the presence or absence of antibacterial activity as a measure of volunteer compliance. The bioassay for serum and urine minocycline concentrations were done using a standard agar diffusion assay employing *Bacillus subtilis* spores, American Type Culture Collection 6633 (14).

**ENG testing.** Prior to the study, 40 of the 89 volunteers had screening electronystagmograms (ENGs) consisting of spontaneous direct current recording from the horizontal leads with eyes closed and bithermal water calorics. Testing was done with a dual channel Instrumentation and Control Systems Incorporated ENG recorder. All sedative medications and alcoholic beverages were discontinued 24 h prior to testing. During the study week, symptomatic volunteers with dizziness, light-headedness, or tinnitus were given complete ENGs, and the tests were repeated on subsequent days if symptoms persisted. We also examined symptomatic volunteers for neurological abnormalities.

The complete ENG examination included spontaneous recordings for horizontal and vertical nystagmus, visually induced eye movements (pendular tracking, optokinetic nystagmus and gaze testing), positional tests, and bithermal water calorics. Except for the visual tests, all recordings were performed with eyes closed. The slow phase velocity for each caloric test was averaged for that ENG, and comparisons were then made between premedication, medication, and postmedication readings. All volunteers with significant abnormalities on ENG during the study period had repeat ENGs performed a minimum of 3 days after the last dose of medication. All ENGs were read before the drug code was broken.

## RESULTS

Table 1 presents the incidence of side effects for men and women volunteers in the minocycline and placebo groups. With the exception of loss of balance ($P < 0.05$), the male subjects did not experience any significant increase in side effects. However, women subjects noted a significant increase in many different symptoms including light-headedness ($P < 0.0001$), lack of ability to concentrate ($P < 0.0001$), loss of balance ($P < 0.01$), nausea ($P < 0.002$), and dizziness ($P < 0.01$). Vestibular symptoms (light-headedness, loss of balance, dizziness, and tinnitus combined) occurred in 70.4% of the women taking minocycline as contrasted with only 9.5% on placebo, a markedly significant ($P < 0.0001$) increase. It was also evident that women taking minocycline had significantly

TABLE 1. *Side effects in placebo and minocycline groups divided according to sex*

| Side effect | No. experiencing side effects with: | | | | P values[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | Minocycline | | | | | |
| | Men ($n$ = 23) | Women ($n$ = 21) | Men ($n$ = 18) | Women ($n$ = 27) | M vs. M | W vs. W | M vs. W | M vs. W |
| Light-headed | 3 (13.0)[b] | 1 (4.8) | 3 (16.7) | 18 (66.7) | NS | <0.0001 | NS | <0.002 |
| Lack of concentration | 1 (4.3) | 0 (0) | 2 (11.1) | 9 (33.3) | NS | <0.0001 | NS | NS |
| Loss of balance | 0 (0) | 1 (4.8) | 2 (11.1) | 9 (33.3) | <0.05 | <0.01 | NS | NS |
| Nausea | 3 (13.0) | 1 (4.8) | 3 (16.7) | 12 (44.4) | NS | <0.002 | NS | <0.05 |
| Dizzy (vertigo) | 2 (8.7) | 1 (4.8) | 1 (5.6) | 9 (33.3) | NS | <0.01 | NS | <0.01 |
| Euphoria | 0 (0) | 0 (0) | 1 (5.6) | 2 (7.4) | NS | NS | NS | NS |
| Vomiting | 1 (4.3) | 0 (0) | 0 (0) | 2 (7.4) | NS | NS | NS | NS |
| Weakness | 1 (4.3) | 1 (4.8) | 2 (11.1) | 1 (3.7) | NS | NS | NS | NS |
| Headache | 4 (17.4) | 3 (14.3) | 5 (27.8) | 7 (25.9) | NS | NS | NS | NS |
| Skin rash | 2 (8.7) | 1 (4.8) | 1 (5.6) | 2 (7.4) | NS | NS | NS | NS |
| Visual problems | 1 (4.3) | 0 (0) | 0 (0) | 2 (7.4) | NS | NS | NS | NS |
| Tinnitus | 0 (0) | 1 (4.8) | 0 (0) | 2 (7.4) | NS | NS | NS | NS |
| Vestibular symptoms[c] | 4 (17.4) | 2 (9.5) | 5 (27.8) | 19 (70.4) | NS | <0.0001 | NS | <0.005 |
| All side effects | 11 (47.8) | 3 (14.3) | 11 (61.1) | 22 (81.5) | NS | <0.0001 | <0.005 | NS |

[a] Four comparisons are presented: men in the placebo group versus men in the minocycline group (M vs. M), women in the placebo group versus women in the minocycline group (W vs. W), men versus women in the placebo (M vs. W), and men versus women in the minocycline group (M vs. W). NS, not significant. $P$ values were computed by a test of proportions using the arc sine transformation.

[b] Numbers in parentheses signify percentages.

[c] Combination of light-headedness, loss of balance, dizziness, and tinnitus.

higher rates of light-headedness, nausea, dizziness, and vestibular symptoms than did men in the minocycline group. Finally, men in the placebo group had a higher rate (47.8%) of all side effects than did women (14.3%) in the same group.

Seventy percent (23/33) of side effects began between the second and third day with 6% (2/33) of side effects occurring in the first 24 h and 24% (8/33) beginning after the third day. Seventy-five percent (18/24) of side effects that continued after stopping the minocycline were gone by 48 h, but 25% (6/24) continued for 3 days or more. None of the volunteers had symptoms disappear before actually stopping the drug.

The symptomatic volunteers in the minocycline group had a significantly longer duration of side effects for all symptoms ($P < 0.01$) and vestibular symptoms ($P < 0.05$) than did the symptomatic volunteers in the placebo group (Table 2). However, the severity of side effects between these two groups did not differ. Four volunteers in the minocycline group and two in the placebo group discontinued their capsules because of severe side effects. Those in the minocycline group discontinued the capsules on day 4 or 5, and all had moderate or severe vestibular symptoms. The two who stopped taking the capsules in the placebo group had an influenza-like illness and, in one volunteer, this was serologically confirmed as influenza A.

There were five volunteers in the minocycline group with positive physical findings while they were symptomatic, and there were none in the placebo group. They included a positive Romberg, slight tremor, slight nystagmus, minimal postural hypotension, and a maculo-papular skin rash. Three volunteers in the minocycline group developed a vaginal yeast infection after the study week with none occurring in the placebo group.

Table 3 demonstrates that there was a significant ($P < 0.02$) fall in the white blood counts of the male volunteers taking minocycline compared with those of the men in the placebo group. The women taking minocycline also showed a decrease in white blood counts, but this change was not significant when compared with those of the women in the placebo group.

TABLE 2. *Analysis of duration and severity code of symptomatic volunteers*[a]

| Determination | All side effects[b] | | Vestibular side effects[b] | |
|---|---|---|---|---|
| | Duration (days) | Severity (days) | Duration (days) | Severity (days) |
| Placebo | 2.21 ± 0.33[c] | 1.43 ± 0.29 | 1.67 ± 0.49 | 1.50 ± 0.50 |
| Minocycline | 3.33 ± 0.17 | 2.00 ± 0.20 | 3.13 ± 0.24 | 1.88 ± 0.23 |
| *P* value[d] | <0.01 | NS[e] | <0.05 | NS |

[a] See text for the duration and severity codes.
[b] Number of volunteers with all side effects: 14 placebo and 33 minocycline. Number of volunteers with vestibular side effects: 6 placebo and 24 minocycline.
[c] Standard error of the mean.
[d] Student's *t* test.
[e] Not significant at the 0.05 level.

TABLE 3. *Minocycline and white blood count (WBC) before and after study period*

| | Pre-WBC/mm³ | Post-WBC/mm³ | Mean Δ | *P*[a] |
|---|---|---|---|---|
| Men | | | | |
| Minocycline (18)[b] | 7,330 ± 2,680[c] (4,300–15,100)[d] | 6,020 ± 1,420 (3,400–9,600) | −1,310 ± 2,766 | 0.02 |
| Placebo (23) | 5,670 ± 990 (4,300–8,300) | 5,780 ± 1,480 (3,100–8,800) | +110 ± 1,119 | |
| Women | | | | |
| Minocycline (27) | 5,640 ± 1,210 (3,600–9,300) | 5,190 ± 1,150 (3,100–7,400) | −450 ± 1,171 | NS |
| Placebo (21) | 6,010 ± 1,430 (4,000–8,700) | 6,050 ± 1,560 (3,700–9,600) | +40 ± 1,426 | |

[a] Two sample *t* tests.
[b] Numbers in parentheses signify number of volunteers in group.
[c] Plus or minus 1 standard deviation.
[d] Range.

Minocycline serum concentrations 1, 2, 4, and 6 h after the ingestion of 100 mg of drug revealed a peak at 2 h (Fig. 1). Serum concentrations demonstrated a progressive increase from day 1 to day 5, and the difference between day 1 and 5 was significant ($P < 0.001$). The mean peak concentration (2 h) for all 3 days in women versus men was significantly different with a higher mean for the women of 3.40 ± 0.33 standard error of the mean μg/ml and a mean for the men of 2.45 ± 0.25 standard error of the mean μg/ml ($P < 0.05$). Correlation of body surface area versus serum concentrations of minocycline revealed an inverse correlation of surface area to serum concentration ($P = 0.01$, Pearson correlation coefficient of −0.6334).

All volunteers in the minocycline group had evidence of minocycline in their urine on a first morning specimen of day 5. Three volunteers in the placebo group also had evidence of antibiotic activity in their urine, but in only one of the volunteers was this activity marked. This volunteer was discovered to have taken rifampin on day 4 of the study after exposure to a patient with meningococcal meningitis. She had no symptoms. The two other placebo urines with minimal antibiotic activity could not be explained.

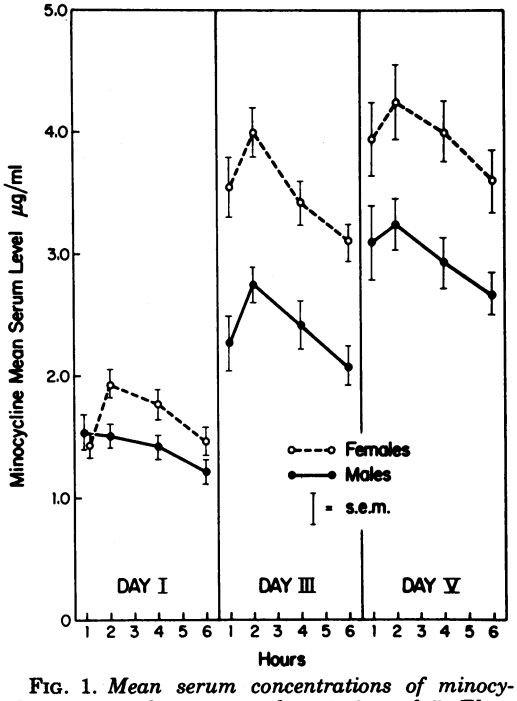


FIG. 1. *Mean serum concentrations of minocycline in 12 volunteers on days 1, 3, and 5. These volunteers received 100 mg of minocycline twice daily for the 5-day period, and the blood samples were obtained at 1, 2, 4, and 6 h after the ingestion of 100 mg of minocycline. The marked increase in serum levels between day 1 and 3 is evident and is a reflection of the 13.5-h half-life of the drug.*

Forty volunteers had screening ENGs prior to the study. All forty had normal bithermal water caloric tests. Twenty symptomatic volunteers had ENGs completed during the study period. Sixteen of the twenty volunteers had only one ENG during the 5-day study period, and four had multiple ENGs during that time. Four volunteers taking minocycline had abnormal ENGs, and all four demonstrated disorganized optikokinetic nystagmus, and three of the four improved in the posttreatment test. One volunteer demonstrated a hyperactive caloric response averaging 29° per s during the treatment phase returning to a normal average response of 18.9° per s after minocycline was stopped. Five volunteers taking minocycline had equivocal ENGs, three demonstrating slightly increased caloric responses and two manifesting equivocal slow spontaneous horizontal nystagmus. The remaining 11 volunteers had normal ENGs including the only individual on placebo. Abnormal ENG readings did not correlate well with neurological findings or severity of side effects, and several volunteers with the most severe vestibular symptoms had normal ENGs. There were too few volunteers who underwent both ENG and serum antibiotic concentration tests to correlate these two measurements.

## DISCUSSION

Previous data on side effects produced by minocycline are confusing. Studies published in 1974 or before showed a low incidence of side effects with minocycline using a short prophylactic regimen (5, 7, 9, 12). The incidence of side effects varied from 0% to 36% with very few vestibular symptoms (dizziness or light-headedness) reported. Reports from 1974 and later showed an incidence of side effects of 73% to 90%, and the majority were vestibular (3, 4, 6, 10, 15). It is difficult to explain the change in the incidence, but differences between the earlier and later studies are apparent.

Most of the earlier studies were done in male, military personnel and were designed mainly to look at eradication of the meningococcal carrier state (5, 9, 15). It is interesting that the study of Devine (5) showed an increase in the frequency of side effects in males when the dosage was increased from 200 mg per 24 h to 400 mg per 24 h, but the frequency did not approach recent figures. A British report stated that side effects in women were 7 to 13 times higher than those in men using 300 mg of mino-

cycline in one dose for gonococcal cervicitis or urethritis (11). In the U.S., using minocycline for meningococcal chemoprophylaxis, one group of observers also noted a higher reaction rate among women than among men, but the difference was not significant (11).

Our data definitely establish that vestibular and other side effects are significantly increased in women taking minocycline. In men, only loss of balance was increased, and this was at a borderline level of significance ($P < 0.05$). It may be that a major explanation for the increase in side effects observed with minocycline is due to the more extensive use in women and also to the greater attention now being paid to side effects.

We observed significantly higher serum concentrations of minocycline in women and feel this may be the explanation for their higher incidence of side effects. The women's higher serum levels are probably related to their smaller size. An analysis of the inverse correlation of body surface area with serum concentrations in the present study confirmed an earlier report of significant differences between peak serum concentrations in men and women when related to body surface area (2). Unfortunately, we determined antimicrobial serum concentrations in too few volunteers to permit an analysis of body surface and sex as independent factors affecting serum minocycline concentrations.

In the present study the men received a mean of 106 mg/m$^2$ per day of minocycline, and the women received 124 mg/m$^2$ per day. Recalculation of a female dosage regimen using the male dose of 106 mg/m$^2$ per day would yield a mean daily dose in women of 170 mg/day. It is not presently known whether reducing the dose in women would decrease the vestibular side effects.

The degree of leukopenia observed in the men in this study was slight but significant. Leukopenia has been associated with tetracycline administration but is rare (13).

The onset of symptoms in the symptomatic volunteers differs from other studies, which reported a high frequency of symptoms within the first 24 h (3, 10). Only 6% of our volunteers had the onset of their symptoms in the first 24 h with the onset occurring most often (70%) between the second and third day. The time of onset may be related to the fact that minocycline serum concentrations increased markedly from day 1 to day 3 (Fig. 1) as would be expected with a drug with a half-life of 13.5 h (2). Most symptoms appear to wane by 48 h (75%) after stopping minocycline, which is in agreement with other studies (10, 15). However, six volunteers had persistence of symptoms for 3 days or more after stopping the medication, and these were the volunteers with the most severe side effects. In two recent studies, a majority of those with symptoms could not complete the course of minocycline because of side effects (10, 15). In our study, only four volunteers in the minocycline group and two volunteers in the placebo group could not complete their medication because of vestibular side effects.

Minocycline has been shown to give levels in canine brains that are higher than doxycycline, tetracycline, or oxytetracycline, and this is probably due to its higher lipid solubility (1). This finding is of interest in view of the vestibular side effects. We used the ENG in hopes of objectively evaluating the vestibular symptoms, but ENG abnormalities were subtle and inconsistent. Forty-seven percent of symptomatic volunteers on minocycline demonstrated normal ENGs. Unfortunately, the ENG did not correlate well with severity of vestibular symptoms; several volunteers with severe symptoms had normal ENGs. The side effects may still be related to the brain levels of minocycline, but minocycline may affect cerebral areas to which the ENG is insensitive. The value of the ENG in predicting ENG abnormalities and the rapid return to normal suggests that the insult to the vestibular system is transient and not particularly severe.

The high frequency of vestibular side effects which we observed in women would argue against the use of minocycline for meningococcal prophylaxis (9). These symptoms might easily confuse the physician looking for the subtle early changes of meningococcal meningitis in the exposed patient. We would agree with the U.S. Public Health Service that rifampin should be used presently until another alternative prophylactic antibiotic is available (10).

## ACKNOWLEDGMENTS

We are indebted to Susan Sykas for technical assistance and to Taka Ashikaga for biostatistical assistance.

This study was supported by a grant from the Parke, Davis & Co., the General Research Support Grant 05429-14 and Public Health Service grant M01 00109-13 from the Clinical Research Center.

## LITERATURE CITED

1. Barza, M., R. B. Brown, C. Shanks, C. Gamble, and L. Weinstein. 1975. Relation between lipophilicity and pharmacological behavior of minocycline, doxycycline, tetracycline, and oxytetracycline in dogs. Antimicrob. Agents Chemother. 8:713–720.
2. Bernard, B., E. J. Yin, and H. J. Simon. 1971. Clinical pharmacologic studies with minocycline. J. Clin. Pathol. 11:332–348.
3. Center for Disease Control. 1975. Vestibular reactions to minocycline after meningococcal prophylaxis. Morbid. Mortal. Weekly Rep. 24:9–11.

4. **Center for Disease Control.** 1975. Vestibular reactions to minocycline – follow-up. Morbid. Mortal. Weekly Rep. 24:55–56.
5. **Devine, L. F., D. P. Johnson, C. R. Hagerman, W. E. Pierce, S. L. Rhode, and R. O. Peckinpough.** 1971. The effect of minocycline on meningococcal nasopharyngeal carrier state in naval personnel. Am. J. Epidemiol. 93:337–345.
6. **Fanning, W. L., and D. W. Gump.** 1976. Minocycline: distressing side effects. Arch. Intern. Med. 136:761–762.
7. **Frisk, A. R., and G. Tunevall.** 1969. Clinical evaluation of minocycline, p. 335–339. Antimicrob. Agents Chemother., 1968.
8. **Guttler, R. B., G. W. Counts, C. K. Avent, and H. N. Beaty.** 1971. Effect of rifampin and minocycline on meningococcal carrier rates. J. Infect. Dis. 124:199–205.
9. **Guttler, R. B., and H. Beaty.** 1972. Minocycline in the chemoprophylaxis of meningococcal disease. Antimicrob. Agents Chemother. 1:397–402.
10. **Jacobson, J. A., and B. Daniel.** 1975. Vestibular reactions associated with minocycline. Antimicrob. Agents Chemother. 8:453–455.
11. **Masterton, G., and C. B. Schofield.** 1976. Vestibular reactions to minocycline – Scotland. Morbid. Mortal. Weekly Rep. 25:31.
12. **Munford, R. S., A. J. Sussuarana de Vasconcelos, C. J. Phillips, D. S. Gelli, G. W. Gorman, J. B. Risi, and R. A. Feldman.** 1974. Eradication of carriage of *Neisseria meningitidis* in families: a study in Brazil. J. Infect. Dis. 129:644–649.
13. **Ory, E. M.** 1974. The tetracyclines, p. 102. *In* B. M. Kagan (ed.), Antimicrobial therapy. W. B. Saunders Co., Philadelphia.
14. **Sabath, L. D., and J. M. Matsen.** 1974. Assay of antimicrobial agents, p. 428–430. *In* E. H. Lennette, E. H. Spaulding, and J. P. Truant (ed.), Manual of clinical microbiology, 2nd ed. American Society for Microbiology, Washington, D.C.
15. **Williams, D. N., L. W. Laughlin, and Y. Lee.** 1974. Minocycline: possible vestibular side effects. Lancet ii:744–746.