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Tolerability of Azithromycin as Malaria Prophylaxis in Adults in Northeast Papua, Indonesia

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Drug tolerability affects compliance. We evaluated the tolerability levels of azithromycin (750-mg loading dose plus 250 mg/day; $n = 148$ subjects), doxycycline (100 mg/day; $n = 75$), and placebo ($n = 77$) as prophylaxis against malaria in Indonesian adults over 20 weeks. Self-reported and elicited symptoms, health perception, hearing, hematology, and biochemistry were assessed. The loading dose was well tolerated. The frequencies (number per person-years [p-yr]) of all daily reported symptoms were similar in the three arms of the study: 40.2/p-yr for azithromycin, 39.7/p-yr for doxycycline, and 38.2/p-yr for placebo. Relative to those who received placebo, azithromycin recipients complained more often of heartburn (rate ratio = 10.5 [95% confidence interval, 2.8 to 88.1]), paresthesia (2.03 [1.08 to 4.24]), and mild (1.55 [1.01 to 2.48]) and severe (11.2 [1.34 to ∞]) itching but less often of fever (0.21 [0.09 to 0.49]) and tinnitus (0.09 [0.04 to 0.21]). Azithromycin recipients showed no evidence of clinical hearing loss or hematologic, hepatic, or renal toxicity. One azithromycin recipient developed an erythematous rash. Daily azithromycin was well tolerated by these Indonesian adults during 20 weeks of treatment.

Prolonged drug use for disease prophylaxis, treatment, or suppression should be well tolerated. This is especially true for healthy recipients of prophylaxis, such as travelers and pregnant women, for whom the risk-to-benefit ratio requires both safe and easily tolerable regimens.

Azithromycin has several clinical indications that include the treatment and prophylaxis of *Mycobacterium avium-M. intracellulare* complex (MAC) infection and the treatment of community-acquired pneumonia and genital or ocular *Chlamydia trachomatis* infection (25). The standard doses of azithromycin (30 mg/kg of body weight for children and 1.5 g total dose for adults) are well tolerated. Up to 12% of patients report any symptom, <10% report gastrointestinal symptoms, and 0.7 to 1.3% discontinue therapy. Such tolerability compares favorably to that of other antibiotics (7, 11, 12, 22). High doses of azithromycin, 1 g/kg for adults and 20 mg/kg for children, are also well tolerated (2, 16). However, doses used for MAC infections (1.2 g/week or 300 to 600 mg/day) are less well tolerated (3, 9, 10, 17). Gastrointestinal symptoms are reported by a high proportion of patients (e.g., by 71 [78.9%] of 85 recipients of weekly azithromycin, resulting in six [7%] withdrawals [17]). Hearing loss in the speech frequency range has also been reported in 13 to 17% of patients with MAC infections. It is dose dependent and recovers within 2 to 11 weeks after discontinuation of the drug (3, 9, 23, 24). Irreversible high-frequency-hearing loss has also been reported following treatment with 750 mg of oral azithromycin in a 37-year-old woman (19). Biochemical and hematological assessments in large clinical series have been unremarkable. Mild elevations of liver enzymes (0.3 to 1.7%) and transient neutropenia (1.5%) or neutrophilia (1.5%) have been documented (11). Significant hepatotoxicity (e.g., hypersensitivity hepatitis, cholestasis) is rare (4, 15), as are anaphylaxis, pseudomembranous colitis, erythema multiforme, and Churg-Strauss syndrome (12, 13, 22).

One trial has previously assessed azithromycin as prophylaxis against malaria. Azithromycin was administered daily (250 mg) or weekly (1 g) for 13 weeks to Kenyan adults. The reported symptoms were similar to those of placebo recipients, and there was no evidence of toxicity on routine hematological or biochemical testing (1).

We report the tolerability of daily-administered azithromycin as prophylaxis against malaria in Indonesian adults.

MATERIALS AND METHODS

Subjects and study conduct. This double-blind, placebo-controlled trial assessed the prophylactic efficacy and tolerability of azithromycin in men and women who had been radically cured (with concurrent quinine doxycycline and primaquine) of any preexisting malaria infection. Details of the study have been reported previously (21). Three hundred Indonesian adults (225 soldiers and 75 villagers) received either (i) azithromycin (750-mg loading dose followed by 250 mg/day) plus a doxycycline placebo ($n = 148$) (arm A), (ii) doxycycline (100 mg/day) plus an azithromycin placebo ($n = 75$) (arm D), or (iii) a double placebo ($n = 77$) (arm P). At the time of witnessed drug consumption, drinking water was provided and sweet biscuits were offered.

This study was conducted in accordance with the Indonesian Ministry of Health, the Indonesian Army, the U.S. Navy, the U.S. Army, and the U.S. Food

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TABLE 1. Incidence rates per person-year by drug arm (azithromycin, doxycycline, and placebo) for all symptoms voluntarily reported daily over the 20 weeks of the trial and significant RR comparisons[a]

Symptom	Azithromycin symptoms (rate)[b]	A vs P RR (95% CI[c])	Placebo symptoms (rate)[c]	D vs P RR (95% CI)	Doxycycline symptoms (rate)[b]
All	1,525 (40.22)		416 (38.22)		852 (39.75)
Gastrointestinal	323 (8.51)		104 (9.55)		161 (7.51)
Anorexia	104 (2.74)		39 (3.58)	0.56 (0.35–0.89)	43 (2.0)
Nausea	53 (1.39)		19 (1.74)		35 (1.63)
Vomiting	11 (0.29)		6 (0.55)		5 (0.23)
Heartburn[d]	73 (1.92)	10.48 (2.79–88.14)	2 (0.18)	6.35 (1.58–55.3)	25 (1.17)
Mild abdominal pain	43 (1.13)		18 (1.65)		25 (1.17)
Severe abdominal pain	2 (0.05)		0 (0)	10.7 (1.14–∞)[e]	10 (0.47)[f]
Diarrhea	34 (0.89)		18 (1.65)		18 (0.84)
Diarrhea, >5/day	3 (0.08)		2 (0.18)		0 (0)
Central nervous system	492 (12.98)		151 (13.88)		278 (12.97)
Mild headache	227 (5.98)		64 (5.88)		119 (5.55)
Severe headache	14 (0.37)		8 (0.73)		7 (0.33)
Dizziness[g]	100 (2.63)		19 (1.75)	2.06 (1.23–3.6)	77 (3.59)
Tinnitus	9 (0.24)	0.10 (0.04–0.21)	27 (2.48)	0.13 (0.05–0.31)	7 (0.33)
Hearing loss	9 (0.24)		5 (0.46)		6 (0.28)
Blurred vision	6 (0.16)		4 (0.37)		7 (0.33)
Paresthesia[d]	78 (2.06)	2.04 (1.08–4.24)	11 (1.01)	0.23 (0.06–0.72)	5 (0.23)
Difficulty sleeping	49 (1.3)		13 (1.2)	1.91 (1.02–3.84)	49 (2.29)[f]
Hallucinations	0 (0)		0 (0)		1 (0.05)
Dermatological	160 (4.22)	1.84 (1.20–2.92)	25 (2.3)	1.65 (1.04–2.69)	81 (3.78)
Mild itching	135 (3.56)	1.55 (1.01–2.48)	25 (2.3)		75 (3.49)
Severe itching[d]	19 (0.5)	11.2 (1.34–∞)[e]	0 (0)		2 (0.09)
Rash	6 (0.16)		0 (0)		4 (0.19)
Miscellaneous	207 (5.46)		71 (6.52)		144 (6.72)
Cough	143 (3.77)		43 (3.95)		94 (4.39)
Fever	11 (0.29)	0.21 (0.09–0.49)	15 (1.38)	0.37 (0.15–0.87)	11 (0.51)
Chills	10 (0.26)		2 (0.18)		5 (0.23)
Sweats	10 (0.26)		4 (0.37)		13 (0.60)
Myalgia	33 (0.87)		7 (0.64)		21 (0.98)
Others	343 (9.05)	1.51 (1.16–2.01)	65 (5.97)	1.47 (1.1–1.98)	188 (8.77)

[a] Person-years of follow-up were 37.91 (arm A), 10.88 (arm P), and 21.43 (arm D).
[b] Values are total numbers of symptoms reported, with incidence rates per person-year given in parentheses.
[c] 95% CI, 95% confidence interval.
[d] A versus D: heartburn RR = 1.6 (95% CI, 1.04–2.7), paresthesia RR = 8.8 (3.6–27.9), and itching (severe) RR = 5.3 (1.3–47.5).
[e] A value of 0.5 was added to the numerator and denominator symptom counts to estimate the RR if the denominator count was 0; 95% confidence intervals were calculated by using the observed data (no adjustment was made to the numerator or denominator).
[f] D versus A: abdominal pain (severe) RR = 8.85 (95% CI, 1.89–83.03), and difficulty sleeping RR = 1.77 (1.17–2.68).
[g] Dizziness and/or muzzy head.

and Drug Administration regulations governing the protection of human subjects in medical research. All subjects in this study gave informed consent.

Assessment and analysis of AEs. An adverse event (AE) was defined as a new symptom, physical sign, or illness that developed during the study; AEs were classified as mild (no interference in activities of daily living), moderate (affecting activities of daily living; treatment required), or severe (bed rest or hospital admission required). Twenty-five common symptoms and less common, "other," symptoms were recorded from two sources: (i) questionnaires administered on days 0 and 1 (loading dose tolerance) and monthly thereafter and (ii) volunteered responses from the subjects to the question asked daily, "Any symptoms?" A health questionnaire was completed at the end of the study. Hearing was assessed (Rinné and Weber tests) at enrollment and at the end of the study. Routine hematology and biochemistry were evaluated at enrollment, at week 4, and at the end of the study.

The sample size was based on the objective of estimating the prophylactic efficacy of azithromycin to rule out a prophylactic efficacy of <70% (80% power, 5% type 1 error, 1 sided) (6). Chi-square analysis and Koopman's method were used to assess differences of independent proportions (14). Incidence rates of daily reported symptoms were compared by using the exact conditional test (5). Days were subtracted if subjects were absent from questioning and/or if they developed malaria (i.e., the 7 days before the day of the positive slide result were subtracted). Laboratory data were analyzed by using analysis of variance or the *t* test (unpaired or paired), as appropriate. Many comparisons were performed; therefore, in Table 1, we decided to show only the results with *P* values of ≤0.05 and 95% confidence intervals for or rate ratio [RR] measures that exclude 1.

RESULTS

The majority of the subjects (286 of 300 [95.3%]) were young males (mean age, 27 years). Enrollment characteristics were similar in the three arms (21). All subjects had normal Rinné tests, but one (in arm A) had Weber lateralization. The median (range) follow-up times in weeks for the different arms were as follows: (i) azithromycin, 14.6 (1.3 to 20.3); (ii) doxycycline, 15.7 (5.1 to 20.3); and (iii) placebo, 7 (0.7 to 18.9). Approximately 97% of all drug doses ingested were witnessed (26,041 of 26,857).

There were eight AEs that necessitated study withdrawal. After 4 weeks of prophylaxis, a 26-year-old soldier on azithro-

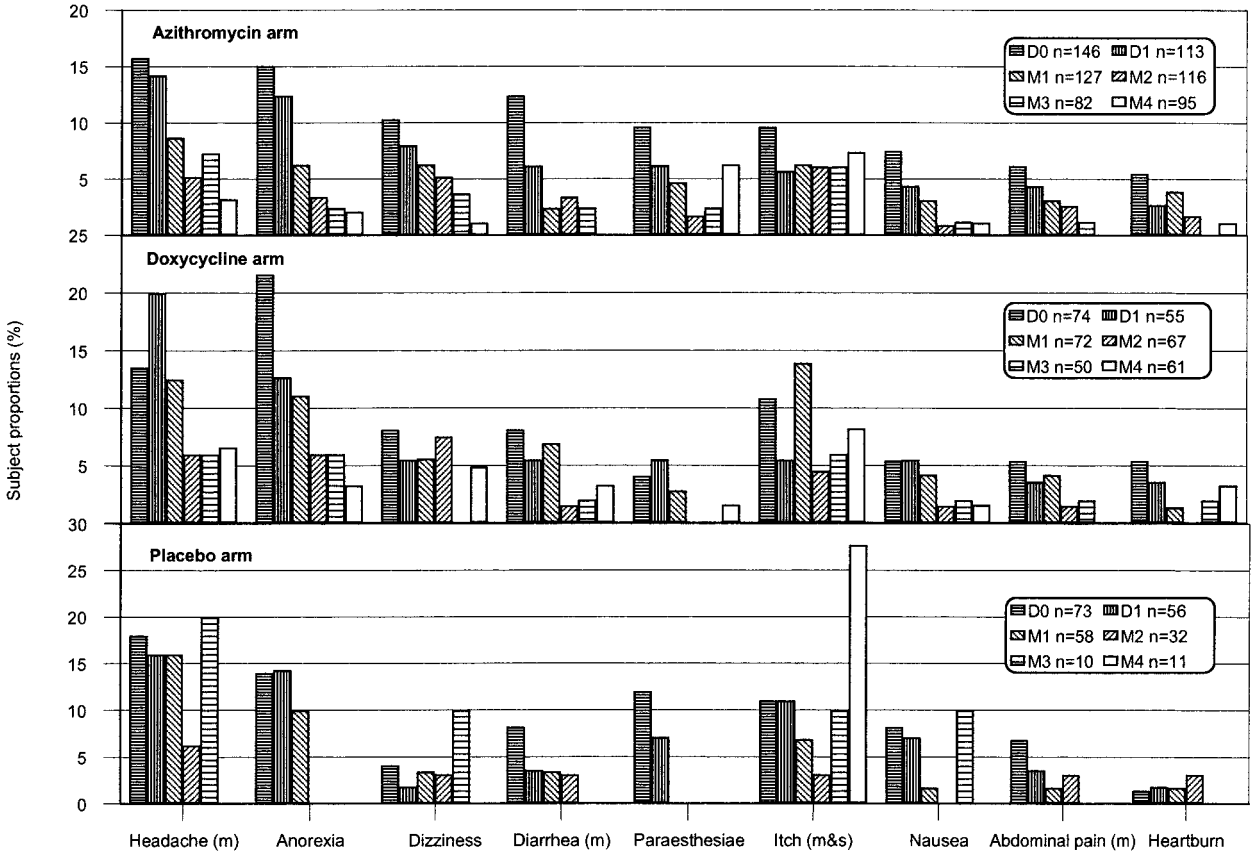

FIG. 1. Trends in selected symptoms as reported by azithromycin, doxycycline, and placebo recipients on a symptom questionnaire on days 0 and 1 (D0 and D1) and at monthly intervals (M1 through M4) during a malaria prophylaxis study in Papua. These elicited symptoms represent an alternative data set to that of the daily volunteered symptoms presented in Table 1. m, moderate; m&s, mild and severe.

mycin developed a widespread, pruritic, erythematous, maculopapular rash, giving a risk of 0.67% (95% confidence interval, 0.034 to 3.29). This moderate AE was considered azithromycin induced. The other seven AEs were all unrelated to the study drugs: ureteric colic, dengue fever, and a motorcycle accident (in arm A); acute bronchitis with hyperventilation and subarachnoid hemorrhage (in arm D); and headache with photophobia and severe malaria (in arm P).

Loading-dose tolerance and monthly reported symptoms. The proportions of subjects who, in response to the symptom questionnaire, reported either a new symptom (i.e., a symptom not present on day 0) or any symptom on day 1 were similar among all three arms (details not shown). Thereafter, several symptoms appeared to show a downward trend in the azithromycin and doxycycline arms, whereas itching appeared to show an upward trend in all three arms (Fig. 1). Discerning trends in the placebo arm is problematic because of the high rate of withdrawal from the study.

Self-reported daily symptoms over 20 weeks: rate comparisons The incidence rates of any self-reported symptoms ranged from 0 to 9.05 symptoms per person-year (p-yr) (a maximum of 9 days over 1 year) (Table 1). Azithromycin recipients reported more heartburn, paresthesia, and severe itching, and doxycycline recipients reported more severe abdominal pain and difficulty sleeping. Subjective hearing loss in participants in any arm was reported with a frequency of <0.5/p-yr.

Self-reported daily symptoms within the first 4 weeks. (i) Proportional comparisons. The percentages of subjects reporting any symptom at least once were similar in the three arms: 58.8% (arm A), 66.2% (arm P), and 61.3% (arm D). Among all the comparisons, only heartburn was an important symptom: (i) arm A versus arm P, 14 of 148 (9.5%) versus 0 of 77 (0%) ($P = 0.005$), and (ii) arm D versus arm P, 7 of 75 (9.3%) versus 0 of 77 (0%) ($P = 0.006$). Subjective hearing loss was reported by nine (3%) participants equally distributed across the three arms (χ^2 [2 df] = 1.1; $P = 0.57$).

(ii) Rate comparisons. The incidence rates of any self-reported symptom ranged from 0 to 7.8/p-yr. The incidences of symptoms per person-year for each arm were 35.8/p-yr (arm A), 37.5/p-yr (arm P), and 38.8/p-yr (arm D). The important symptoms in the azithromycin recipients, versus those in the placebo recipients, were heartburn (2.41 versus 0/p-yr; RR = 25.7 [95% confidence interval, 3.19 to ∞]) and myalgia (1.70 versus 0.19/p-yr; RR = 8.88 [1.41 to 368.9]). For doxycyline recipients, the important symptoms were heartburn (2.26 versus 0/p-yr, RR = 24.6 [2.77 to ∞]), myalgia (1.56 versus 0.19/p-yr, RR = 8.19 [1.14 to 358.8]), and difficulty sleeping (6.26 versus 1.91/p-yr, RR = 3.28 [1.59 to 7.40]). Subjective hearing

loss in participants in any arm was reported with a frequency of <0.53/p-yr.

Health questionnaire and hearing at study end. The health questionnaire was answered by 257 of 300 (85.6%) subjects. The majority of subjects (94.9% [244 of 257]) reported feeling healthier than they had felt at the start of the study. The proportions of subjects who recollected experiencing nausea and/or vomiting, diarrhea, or hearing impairment at any time during the study were 25.3% (65 of 257), 23.3% (60 of 257), and 5.1% (13 of 257), respectively; all proportions were not significantly different between the three arms (details not shown). Weber lateralization was detected in 7 (2.7%) of 262 subjects: 3 of 132 (2.3%) in arm A, 2 of 64 (3.1%) in arm D, and 2 of 70 (2.8%) in arm P (χ^2 [2 df] = 0.14; $P = 0.57$). All had normal Weber tests at enrollment.

Laboratory evaluations. Mean biochemical and hematological values at day 0, week 4, and the end of the study and their mean changes (values at study end minus values at day 0) were not significantly different between each drug arm and placebo (details not shown). Proportions of subjects with elevated aspartate transaminase (AST) levels (>40 IU/liter) at enrollment (17 of 300 [5.6%]), 1 month later (23 of 265 [8.6%]), and at the end of the study (14 of 154 [9.1%]) were not significantly different from each other ($P = 0.28$). Nine (6.2%) of 145 subjects with normal day 0 AST levels had mildly elevated values at the end of the study: (i) arm A, 41 to 50 IU/liter ($n = 6$), and (ii) arm D, 41 to 63 IU/liter ($n = 3$). Total white cell counts were unremarkable during follow-up: for azithromycin recipients, ≥4,500/μl, and for doxycycline recipients, ≥4,400/μl.

DISCUSSION

Azithromycin administered daily for up to 20 weeks was well tolerated by the Indonesian adult study participants and did not appreciably affect their routine hematological or biochemical measurements. Doxycycline was also well tolerated.

Clinicians assess drug toxicity by evaluating symptoms in the context of the patient's past medical history, drug history, the local disease epidemiology, physical signs, and pertinent investigations. By contrast, clinical trials focus primarily on broad assessments involving group comparisons, and these trials benefit from blinding. We have analyzed a large amount of data over 20 weeks and considered some of the issues inherent in such an analysis. We have reported symptom data as proportions and rates. Proportions are an indication of how many subjects report symptoms within a defined period of equal risk. Rates are an indication of how often these symptoms are reported. The differential attrition in the placebo arm precluded comparisons of risk, relative risk, and symptom trends over 20 weeks; therefore, risk analysis was confined to the first 4 weeks of follow-up. Analysis by incidence rates takes into account the unequal follow-up times but cannot determine whether many symptoms are reported by few subjects or vice versa (8). The second issue involves the interpretation of results obtained from multiple statistical comparisons. Determining which symptoms are important or whether differences exist based on simple hypothesis testing is challenging because of the possibility of overreporting (type I error) or failing to detect (type II error due to adjusting P values) significant symptoms (18). Cognizant of these issues, and with the view that analysis of complex symptom data are largely exploratory, we flagged only those comparisons where the P value was ≤0.05.

The most important AE was an azithromycin-induced maculopapular rash in one subject that was classified as moderate in severity. The reported risk of a rash with azithromycin from large clinical series is low at ≤1.1% (11, 12, 22). Several other symptoms were noteworthy. Heartburn, a well-recognized effect of doxycycline (20), was also reported but at a lower frequency than in the azithromycin group. In azithromycin reports, heartburn is often not reported separately from abdominal pain, making it difficult to put our heartburn data into context. At 4 weeks, itching, paresthesia, and subjectively severe abdominal pain were unremarkable. However, over 20 weeks, itching and paresthesia were reported more frequently by subjects in the azithromycin arm (versus placebo) and severe abdominal pain was reported more frequently by subjects in the doxycycline arm (versus placebo), suggesting that these symptoms emerged gradually. At 4 weeks, myalgia was reported more frequently by subjects in both drug arms but not over 20 weeks, suggesting that it developed acutely but was tolerated over time. Hearing loss was reported infrequently. At the end of the study, signs consistent with a sensineural hearing loss were detected in a small number (2.6%) of subjects from all three arms. Despite the limitations of tuning fork hearing assessment relative to audiometry, these signs are unlikely to represent appreciable auditory nerve pathology. Azithromycin-induced hearing loss generally improves with drug discontinuation or dose reduction, but clinicians should be aware that irreversible hearing loss has been reported (19). No azithromycin recipient developed leukopenia as has been reported in other studies (4, 16). A small proportion of azithromycin recipients developed mild elevations of AST by the end of the study; the peak value was 50 IU/liter. This modest increase is of doubtful clinical significance, but we cannot exclude the possibility of a mild, drug-induced hepatitis.

Our trial evaluated azithromycin in predominantly healthy and fit young soldiers under field conditions in a tropical environment. Our findings cannot be extended with confidence to children, women, pregnant women, and patients with AIDS. The small sample size precluded the detection of rare and possibly serious side effects.

The prophylactic efficacy of azithromycin against falciparum malaria was considered too low, ~72%, to recommend it as a first-line prophylactic agent (21). However, azithromycin's antimalarial properties could be useful in drug combinations. Tolerability data from this study support further studies with azithromycin.

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