Tolerability and Effectiveness of Malaria Chemoprophylaxis with Mefloquine or Chloroquine with or without Co-medications

Jürg C. Handschin, Michael Wall, Robert Steffen, and Dieter Stürchler

Background: To determine the relevance of drug interactions with co-medication for effectiveness and tolerability of antimalarial chemoprophylaxis.

Method: A database (MALPRO2) on travelers on their flight home from Africa to Europe between July 1988 and December 1991 was reanalyzed. It contains data on prophylaxis with mefloquine (n = 48,264), with chloroquine (6,752), with chloroquine plus proguanil (19,727), and with no prophylaxis (3,871). The comparison of rates of malaria incidence and adverse events (AEs) between users and nonusers of co-medication was expressed by relative risk (RR).

Results: Fifty-three percent of travelers (63% of females, 43% of males) used co-medication in all prophylaxis groups, with an average of 1.35 additional drugs per person and about two AEs reported per person. With the exception of antidiarrheals plus mefloquine, malaria incidence with co-medication was lower (RR = 0.8) than without co-medication. In all regimens, the proportion of travelers reporting AEs was about 1.5-fold with co-medication (p<0.01); that reporting severe AEs was twice as high as compared to no co-medication. Mefloquine AE rates for various classes of co-medication were similar to that of chloroquine, with highest AE and severity rates with neuropsychiatric drugs (excluding antiepileptics, RR = 1.9 and 2.9), and lowest rates with cardiovasculars (RR = 1.1 and 1.0). Various co-medications were used with different frequencies in males and females, and the latter reported more AEs.

Conclusion: These data suggest that co-medications commonly used by travelers have no significant clinical impact on safety and effectiveness of prophylaxis with mefloquine or chloroquine. Increased frequency and severity of AEs when using co-medication rather is explained by underlying illness.

The use of several medications is common, for instance in travelers on antimalarial chemoprophylaxis. Much has been published on pharmacokinetic or pharmacologic drug-drug interactions under laboratory conditions, particularly for mefloquine. However, there seem to be no data on the practical relevance of drug interactions in the field.

A database containing some of the required data made such evaluation possible. Concomitant use of other drugs with mefloquine was of particular interest, because of its much publicized adverse events (AEs) and its wide recommendation as first choice prophylaxis in areas with drug-resistant falciparum malaria. The use of chemoprophylaxis in senior travelers is a specific aspect where co-medication is of concern.

Subjects and Methods

An existing database, MALPRO2, was used. Between July 1988 and December 1991, self-administered questionnaires (Q1) were completed by travelers on their flight home from East Africa to Europe, and a follow-up questionnaire (Q2) was completed 3 months after return. Answers from Q1 and Q2 were combined. Reports of malaria or of serious adverse events were followed up with the treating physician. Four groups of the population were analyzed according to whether they had used mefloquine; chloroquine 300 or 600 mg/week (C300/600); or chloroquine plus proguanil (C+P); or no prophylactic antimalarial (no Px). The subpopulations were further stratified into those having and those not having used co-medication.

Of a total of 100,278 travelers in the dataset, 21,664 (21.6%) were excluded from evaluation (multiple reasons possible) because of (1) use of other prophylactic antimalarials (19.0%); (2) change of prophylactic regimen during the observation period (2.9%); (3) use of stand-by antimalarial treatment (0.7%) (not excluded for assessment of effectiveness); or (4) a stay abroad of > 3 months (0.6%). Subpopulations (2) and (3) were excluded, as the AEs reported could not be allocated clearly to one prophylactic antimalarial or the other. Changes in the regimen, among
them about 40% for perceived adverse drug reactions to chemoprophylaxis, were equally frequent in those who used chloroquine alone or mefloquine, but were about 1.5 times more frequent in those who used C+P.

The most important questions in Q1 (and Q2) for this evaluation were: “Have you noticed anything that you believe might be a side effect of a drug you have been taking as prophylaxis against malaria?”; “Which side effects did you experience?”; and (Q1 only) “Did you take any medication other than antimalarial drugs while in Africa?” Other questions addressed potential incapacitation due to AEs or illness, and effectiveness of the regimen. For practical purposes, most of the individual symptoms or co-medications were grouped into a few classes for analysis. Because a causality assessment of reported “side effects” with drug use was not possible in the survey, and because feedback on perceived untoward effects of co-medication was not sought, the neutral term “adverse event” (AE) will consistently be used when tolerability is addressed, unless a potential causality is implied (“adverse drug reaction”). Checkboxes in the questionnaires allowed subjective rating of AE severity (mild, moderate, severe). If the same AE, but with different severities, was reported in Q1 and Q2, it was counted once, with its highest severity. No correction was made for background AE rates reported by travelers not having used chemoprophylaxis. For assessment of effectiveness, only reports confirming parasitemia by blood smear were considered.

Results are presented in the form of rates or proportions, and rate proportions in the form of relative risk (RR). For statistical analysis of AE rate differences, chi-squared ($\chi^2$) testing was used, and differences with $p<.01$ were considered statistically significant. To statistically analyze differences between malaria incidence, a multiple regression model, which considered the influence of co-medication, prophylaxis, duration of stay in Africa, and compliance with prophylaxis, was used.

Table 1  Characteristics of the Study Population

<table>
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<tr>
<th>Weight Classes</th>
<th>% Males</th>
<th>%</th>
<th>% Females</th>
<th>%</th>
<th>Approx avg age (years)</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>Avg stay abroad (weeks)</th>
<th>n for malaria incidence*</th>
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<td>44</td>
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*includes those having used stand-by treatment

Study Population and Details of Co-medication Intake

Basic data of the study population of 78,614 travelers are given in Table 1. The three prophylaxis groups were remarkably similar in the proportion of those who used co-medication, in that females used far more co-medications (mainly oral contraceptives) than males, in that the average age was from 37–39 years, and in that the average length of stay abroad was from 2.2–2.4 weeks. Those who used no chemoprophylaxis had less co-medication, while all other basic data were comparable. In the various groups, 50–57% of travelers indicated “regular” use of co-medication, the remaining proportion “occasional” use. In those with co-medication, the average number of additional drugs used was about 1.35 in all groups.

Co-medication and Malaria Incidence

As shown earlier, the incidence of malaria was lowest in users of mefloquine prophylaxis. Cumulative exposure to malaria risk varied between 4,107 (C300/600) and 28,578 (mefloquine) personmonths. A negative effect of co-medication on effectiveness of antimalarial prophylaxis was not detected. Rather, the opposite was consistently found with all prophylactic regimens assessed: a slightly enhanced effectiveness of prophylaxis in co-medication users vs. nonusers (RR of malaria incidence = 0.8), although differences were not statistically significant when analyzed with the multiple logistic regression model. A compliance effect with chemoprophylaxis could not be identified. On the other hand, in the subgroup of travelers using antidiarrheals (29–31% in the various regimens), a trend for lower effectiveness of mefloquine was observed (RR of malaria incidence=1.2).
Co-medication and Adverse Events Compared between Prophylactic Regimens

In all regimens, AEs were about 1.5-fold more frequent in the co-medication groups than in the non-co-medication groups, whether the frequency of AEs in non-co-medication users was low (3%) as in the no-Px group, or high (28%) as in the C+P group (p<.01 for all regimens) (Table 2). Thus, AE frequencies increased not additively, but proportionally over baseline in the co-medication groups. The same applied to the proportion of travelers with severe AEs, where the RRs of with vs. without co-medication ranged between 2.0 and 2.2 (significant in the mefloquine group: p<.01). This indicates that the use of co-medication was correlated not only with a higher frequency of AEs, but also with relatively higher severity. Even larger differences of 2.3- to 2.5-fold were observed for the rate of travelers visiting a doctor or requiring hospitalization in all prophylactic groups (p<.01 for mefloquine and C+P), whereas the rate of those who discontinued prophylaxis did not differ in the C300/600 group.

Figure 1 demonstrates that the proportional increase of AE frequency with co-medication was also observed in the various classes of AEs, as individual RRs did not vary much and were very similar in mefloquine and chloroquine users. Although the figures of no Px cannot be judged due to low user numbers, they are included for comparison. Contrary to those RRs, little varied among various AE classes in the two chemoprophylaxis groups, and individual classes of co-medication were associated with a variety of relative changes of AE rates (Fig. 2). The patterns for mefloquine and chloroquine were again almost identical (numbers for no Px were too low for reasonable comparison). Antidiarrheals were by far the most frequently used single co-medication.

Mefloquine users reported a rate and severity of AEs which significantly correlated with the number of co-medications taken: 35% for multiple vs. 26% for single co-medication users reported AEs (RR compared to no co-medication = 1.8 vs. 1.4, p<.01). The rate of severe AEs also increased with multiple co-medication: 6.7% vs. 3.6% users reported severe AEs (RR = 3.3 vs. 1.8, p<.01). Neuropsychiatric drugs were associated with the highest increases (RR = 1.9, p<.01, RR severe AEs = 2.9). No increase in the AE rate and severity was observed with cardiovascular drugs, such as β-blockers (RR = 1.1 and 1.0, p>.05). RRs of AE rates with analgesics, antiinfectives or antidiarrheals all ranged between 1.3 and 1.6 as compared to no co-medication (all p<.01), with RRs for severe AEs between 1.6 and 2.9 (for antidiarrheals p<.01). The significantly increased risks for AEs and their severity associated with contraceptives

**Table 2 Co-medication and AEs by Prophylaxis Groups: Rates, Severity and Consequences of AEs**

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<th>Prophylaxis groups</th>
<th>n</th>
<th>% w/AE</th>
<th>RR AE</th>
<th>% w/severe AE</th>
<th>RR severe AE</th>
<th>% discontin Px for AE</th>
<th>RR discontin Px for AE</th>
<th>Avg no. AE/pers. w/AE</th>
<th>RR avg no. AE/pers. w/AE</th>
<th>n</th>
<th>% w/AE</th>
<th>RR AE</th>
<th>% w/severe AE</th>
<th>RR severe AE</th>
<th>% discontin Px for AE</th>
<th>RR discontin Px for AE</th>
<th>Avg no. AE/pers. w/AE</th>
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**Figure 1.** Co-medication and classes of AEs by prophylaxis groups. The bars show the percentage of travelers with AEs in the co-medication subgroup. The insert shows the relative risk for AEs in co-medication users (+) vs. nonusers (−).
When classes of AEs in the mefloquine group were examined in relation to classes of co-medication exclusively used, significant rates (p<.01) were reported for neurologic AEs (e.g., headache) when analgesics were used, for psychiatric AEs with neuropsychiatric drugs, and for nausea with antidiarrheals (Fig. 3). There was a trend for more nausea with antineoplastics.

Among 54 travelers who took mefloquine plus antiepileptics alone or with additional co-medication, 8 (15%) reported AEs, a rate lower than that without co-medication (19%), with half of the AEs being severe (4 cases, p>.05). One of the severe cases reported seizures and hospitalization, whereas the other AEs were not neurologic nor was medical help sought. Among 37 travelers who used mefloquine plus quinolones alone or with other co-medication, 12 (32%) experienced AEs, two of them (5.4%) severe ones, none of the latter needing medical help. These rates were thus similar to those with mefloquine taken with other antiinfectives. Forty-four travelers reported the exclusive use of mefloquine plus anticoagulants, of whom 6 (14%) experienced AEs, none severe. Of 71 travelers reporting exclusive use of mefloquine plus antidiabetics, 13 (18%) experienced AEs, 3 of them (4.2%) reporting severe ones. This latter rate is 2-fold higher than that with no co-medication (2.1%, p>.05), although the overall AE rate was not different.

Stratification of the mefloquine group for gender revealed that 25-6596 more women than men reported AEs, depending on the type of co-medication used (RR AE M/F = 0.6-0.8) (Fig. 4). It appears that neuropsychiatric drugs were preferably used by women (ratio M/F = 0.5), whereas antiinfectives and antidiarrheals were more common with men (ratio M/F = 1.7 and 1.8). The use of analgesics and cardiovascular drugs was similar in both genders.

**Discussion**

The MALPRO database provides an opportunity to compare safety and effectiveness of antimalarials at the prophylactic dose level in travelers with or without use of co-medications, but there are limitations in this
retrospective dataset. The survey was designed neither to investigate the effect of co-medication on tolerability, effectiveness or pharmacology of malaria chemoprophylaxis, nor to analyze specific AEs or chemical entities of co-medication. Also, it is disturbing that some travelers not using prophylaxis reported perceived adverse drug reactions of antimalarials, with an AE profile similar to that of the real chemoprophylaxis users.

In the MALPRO data, there was no major difference in reported tolerability between mefloquine and chloroquine. This also applies when common co-medications are used.

Since no temporal sequence of AEs could be analyzed, the observed correlation between rates of AE classes and classes of co-medication (see Fig. 3) allows for two main hypotheses: (1) that use of co-medication could be a consequence of AEs experienced, e.g., analgesics to treat headache, which could be travel-related or an adverse drug reaction to malaria prophylaxis (post-effect co-medication); (2) that a proportion of travelers used, for example, sedatives or antidepressants prophylactically more or less regularly because those people were susceptible to travel-related stress or had concomitant diseases (not assessable with the database) (pre- and post-effect co-medication). Co-medications also cause adverse drug reactions. A third, much less likely, explanation would be that the increased AE rate with co-medication would mainly be due to negative interactions between antimalarial and co-medication (pre-effect co-medication).

Co-medication overall did not result in an additive increase of AE rates, but in a proportional increase of about 50% over the baseline rate seen with any regimen alone. This is best illustrated by comparing the no Px group (lowest AE rate) with the C+P group (highest AE rate). This finding is not easy to explain, because the proportion of travelers taking co-medication was, with the exception of the no Px group, almost identical in the various prophylactic regimens; the average number of co-medications in those who indicated intake of other drugs was very similar in all groups assessed; and the average number of AEs in travelers reporting AEs was not higher in groups with high AE rates. The most likely reason is that co-medication was indeed taken for expected benefits including the treatment of reported AEs (post-effect co-medication), and would also explain the higher degree of AE severity in co-medication users. This means that a selection for travelers using co-medication is automatically a selection for higher AE rates. Rather, a constant additive increase would be expected at identical intensity of co-medication use, had co-medication itself or drug interactions caused the increased AE rates (pre-effect co-medication).

With neuropsychiatric drugs, an interaction of mefloquine at the cellular receptor level is unlikely to contribute to an increased AE rate, as the binding of the drug to relevant nervous cell receptors is minimal, similar to low benzodiazepine and GABA receptor binding of chloroquine. No clustering of concomitant drug class was seen in a review of neuropsychiatric AEs with mefloquine.

Those also using antiepileptics had no increased AE rate, but severity was markedly above average. One of the four severe AEs was a seizure and required hospitalization. In view of 20-30% of epileptic patients experiencing seizures despite treatment, and of 8% needing hospitalization, it is well possible that this case was a spontaneous event, unrelated to the use of mefloquine prophylaxis. Nevertheless, mefloquine remains contraindicated in travelers with a history of seizures, the more so because a direct drug interaction of mefloquine with a commonly prescribed antiepileptic, valproate, has been reported.

Cardiovasculars, for example β-blockers, did not reveal any problems as co-medication of mefloquine. Roche drug safety monitoring points in the same direction, and mefloquine itself in prophylactic doses was found not to induce clinically relevant ECG changes. Experimental studies in dogs and rats did not show any pharmacodynamic interaction between mefloquine and β-blockers. The contraindication of concomitant use of β-blockers and other cardiovascular drugs in the former Lariam product information was therefore removed. Similarly, with quinolones the AE rate and severity didn’t differ from that with other antibiotics, nor had Roche drug safety monitoring indicated that an interaction might occur. A corresponding precaution statement, included originally for theoretical reasons, appeared no longer justified.

Whereas the data with anticoagulants do not suggest clinically relevant interactions with mefloquine, an increased severity rate of AEs occurs with antidiabetics. Even though the overall AE rate was not different from that with no co-medication, caution is advised in using mefloquine in diabetic travelers, as the hypoglycemic effect of quinine is well known, and appears possible also with mefloquine under special circumstances.

Females reported AEs more often than males. Similar findings were made in a mefloquine tolerability study, in a survey on mefloquine and doxycycline prophylaxis in travelers from Australia, and in retrospective analyses of neuropsychiatric AEs with mefloquine. Apparently, female–related overreporting of AEs can be explained neither by the lower average body weight of women with consequent higher relative drug dosage, nor by significant sex-differences in the pharmacokinetics of mefloquine. Possibly women may more spontaneously admit inconveniences or worries, as observed with other medication. One may assume
that the higher rate and severity of AEs reported with contraceptives vs. no co-medication is also gender-related. Pharmacokinetic interaction between contraceptive steroids and mefloquine or chloroquine was not found.28-30 The more frequent use of neuropsychiatric drugs by females is in line with earlier findings,27 while the higher proportion of males using antiretroviral drugs or antidepressants on the other hand may possibly be explained by increased risk-behavior, such as consumption of unsafe food or alcohol or participation in casual sex.

Alcohol, probably the most frequent and relevant “co-medication,” was not covered in the survey. Although binge drinking has been suggested to precipitate severe psychiatric reactions in combination with mefloquine prophylaxis,30 a recently published, well-controlled study demonstrated that this combination, at least at low blood alcohol concentration, has no negative impact.31

So far, no data exist on the influence of co-medication on efficacy of antimalarials. The present analysis demonstrates a favorable effect. Whether this was related to a better compliance with antimalarial prophylaxis could not be concluded from the data. With antidiarrheals, effectiveness of prophylaxis with mefloquine only might have been reduced slightly. Diarrhea following mefloquine therapy is a known risk factor for treatment failure with mefloquine.32 This effect is related to reduced mefloquine blood levels,33,34 possibly due to interference with suggested enterohepatic recycling of mefloquine,35 a pathway apparently not investigated with chloroquine. Chloroquine absorption was found not to be affected by diarrhea, whereas proguanil absorption was slightly decreased.36 Thus, not antidiarrheals, but rather the underlying disease, could possibly reduce prophylactic efficacy of mefloquine.

In conclusion, although use of co-medication is correlated with higher AE rates of prophylactic antimalarials, one may assume that co-medications commonly used by travelers in general have no significant clinical impact on safety and effectiveness of prophylaxis with mefloquine or chloroquine. Increased frequency and severity of AEs in co-medication users is better explained by the reason for use of co-medication than by the consequence of such use. However, the potential for adverse drug reactions of co-medication itself as well as a few specifically described drug interactions must nevertheless be considered.

Acknowledgments

Our thanks to Ms Marion Segato and Mr. Bruno Rieser for artwork assistance.

References

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