Physical and mental fitness of pilots is a prerequisite for flight safety. Moreover, airlines’ occupational medicine departments have an obligation to prevent work-related illness. The risk for aircrew flying to areas of high malaria transmission has been estimated at 0.5 per 1,000 persons per stay overnight. However, there is a considerable variation in risk, depending on the degree of endemicity in the area visited, the duration of stay, individual behavior, and preventive measures taken. Risk is especially high in tropical Africa, where 80 to 95% of infections are caused by *Plasmodium falciparum*. Fatal cases in aircrew have been reported, and in nonfatal cases, considerable periods of incapacity have been described. In some cases onset of symptoms may occur in a pilot during the performance of duties, which may lead to acute incapacitation. Last year an increase was observed in cases of Dutch aircrew who contracted malaria in Abuja and Lagos (Nigeria), Accra (Ghana), Dar es Salaam (Tanzania), and Douala (Cameroon). To protect aircrew flying to malaria-endemic destinations, effective and safe prophylactic medication should be provided in addition to education of individual measures to prevent mosquito bites.

Effective prophylaxis of falciparum malaria in aircrew has been hindered by resistance of *P. falciparum* to prophylactic drugs, noncompliance with prophylactic regimens, and potentially adverse effects of prophylactic medication affecting pilot performance. At present, resistance of *P. falciparum* to chloroquine, which used to be the recommended prophylaxis in aircrew, is widespread in all regions of Africa, South America, and Asia, and mefloquine resistance is of growing concern in Southeast Asia. In past decades, compliance of aircrew with any prophylaxis has been poor. Some airlines reported that only 7% of their personnel at risk took their prophylactic drugs as prescribed. Noncompliance in aircrew is a result of multiple factors. Chloroquine or doxycycline prophylaxis necessitates continuation of treatment.

**Malaria Prophylaxis for Aircrew: Safety of Atovaquone/Proguanil in Healthy Volunteers under Aircraft Cabin Pressure Conditions**

*Ries Simons, Pierre J.L. Valk, and Arno J. Krul*

**Background:** Because malaria in endemic areas presents a serious threat to the health of aircrew, optimal prevention is important. An effective and safe prophylactic antimalarial drug is needed. The combination of 250 mg atovaquone with 100 mg proguanil HCl (atovaquone/proguanil, or A/P) has shown good prophylactic efficacy and tolerance for prevention of falciparum malaria. However, medication for use by aircrew on duty is subject to approval by national and international aviation authorities, who require convincing evidence that the treatment has no negative effects on the flight performance of crews.

The purpose of the present study was to evaluate the risk of detrimental effects of atovaquone/proguanil on flight-related performance and alertness in healthy subjects under conditions of aircraft cabin pressure.

**Methods:** A randomized, double-blind crossover study was conducted in which 24 subjects were enrolled to use A/P and placebo, each in a 14-day prophylactic dosing regimen with a 21-day washout phase. Vigilance, alertness, complex information processing, and sleepiness were assessed in a hypobaric chamber at 75.2 kPa, which equals the lower limit of commercial aircraft cabin pressure. Furthermore, duration and quality of sleep at home were recorded during the 14 days of drug administration.

**Results:** Twenty-two subjects completed the study. No significant differences were found between the effects of placebo and A/P on vigilance, alertness, complex information processing, sleep duration and quality, and the occurrence of adverse effects.

**Conclusions:** In-flight performance and alertness of aircrew will not be affected by the prophylactic use of A/P during a period of 14 days.
for 4 weeks after departing from malaria-endemic areas. Consequently, aircrew flying more than once in 5 weeks to endemic destinations have to take this prophylaxis year-round for many years; hence, they stop taking it. On the other hand, aircrew flying only seldom to malaria-endemic regions easily forget to take proper prophylaxis.

Most of the currently recommended malaria prophylactics potentially have disadvantages concerning flight performance or health of aircrew. Although it has been proven that mefloquine does not affect flight performance, it may cause neuropsychiatric effects, which preclude the prophylactic use of this drug by pilots. Moreover, cases of arrhythmia have been associated with mefloquine, which is an additional caveat in the case of aircrew. Doxycycline has disadvantages for airline crew, who would have to use this broad-spectrum antibiotic continuously for many years. Adverse effects may include photosensitivity, diarrhea, and candidiasis. Chloroquine prophylaxis may lead to effects such as nausea, headache, and pruritus, and there are fears, whether realistic or not, regarding long-term adverse effects such as alopecia, corneal opacity, retinopathy, and deafness. An appropriate prophylactic for commercial aircrew should be highly effective against falciparum malaria, have a simple and short dose regimen, and be void of impairing effects on pilot performance.

Recently, the combination of 250 mg atovaquone and 100 mg proguanil HCl has shown good prophylactic efficacy for the prevention of falciparum malaria, including those infections acquired in areas with chloroquine-resistant strains. The most common adverse effects reported in travelers using atovaquone/proguanil (A/P) for prophylaxis or treatment are abdominal pain, nausea, vomiting, and headache. Recent studies indicate that A/P prophylaxis was associated with significantly fewer neuropsychiatric adverse effects than mefloquine. A/P provides causal prophylaxis; therefore, aircrew can stop taking it 1 week after leaving an endemic area, which will facilitate compliance. This makes this agent a promising candidate prophylactic for use in aircrew.

However, use of medication for aircrew on duty is subject to approval by national and international aviation authorities, who require convincing evidence that the treatment concerned has no negative effects on flight performance of the crew. Piloting modern aircraft requires complex psychomotor coordination, high rates of information processing, and high-speed decision making. On the other hand, during prolonged operations, pilots have to sustain attention and maintain vigilance under relatively monotonous conditions. These capacities are particularly vulnerable to drugs causing impairment of cognitive functioning and alertness. Moreover, the effects of drugs might be potentiated by mild hypoxia, which is a consequence of the lowered ambient pressure that prevails in a modern aircraft cabin. Ambient pressure in aircraft cabins ranges between 81.2 and 75.2 kPa, which corresponds with atmospheric pressures at altitudes between 1,830 and 2,440 m (6,000 and 8,000 ft.). It has been shown that this lowered pressure causes mild hypoxia in aircrew and passengers (oxygen saturation of hemoglobin 89–93%) and may result in impaired performance. Therefore, our standard requirements for studies of the effects of medication on flight abilities include exposure of subjects to the minimum allowable cabin pressure (75.2 kPa) during test sessions.

In the case of A/P prophylaxis, the only study assessing the effects on cognitive performance was performed by Paul and colleagues, who found no effects on serial reaction time, logical reasoning, serial subtraction, or multitask performance at the end of a 7-day dosing protocol with A/P daily. However, this study did not take into account the effects of the lower ambient pressure prevailing in the work environment of aircrew. Moreover, steady-state blood levels of A/P are anticipated to be reached after 14 days (A. Miller, personal communication, October 2002), whereas the study of Paul and colleagues covered 7-day dosing.

To enable aeromedical decision making on approval of the use of A/P prophylaxis by aircrew, the present study was designed to evaluate the risk of detrimental effects of A/P on flight-related performance and alertness in healthy subjects under conditions of simulated cabin pressure.

Methods

Study Design and Medication

This study involved a randomized, double-blind, placebo-controlled, crossover trial. Doses of 250 mg atovaquone with 100 mg proguanil HCl and matching placebo were randomly assigned to qualifying subjects. Each dose of study drug was orally administered with 150 mL of milk, yogurt, or custard on each day of a 14-day treatment period. All subjects received both study treatments with a 21-day washout period between treatment phases (more than five times the half-life of A/P). The study was approved by the Medical Ethical Review Committee of the Foundation for Therapeutic Evaluation of Drugs (Stichting Therapeutische Evaluatie Geneesmiddelen, Duivendrecht, The Netherlands) prior to the start of the study.

Subjects

Twenty-four healthy subjects (14 male and 10 female) entered the study after they had been fully informed about the objectives, procedures, and risks of study participation and after signing a written informed consent form.
They had a mean age of 22.9 years (SD 5.8 yr), a mean weight of 70.1 kg (SD 11.9 kg), and a mean height of 178 cm (SD 9.2 cm). Before being accepted into the study, all subjects underwent a medical screening designed to preclude participation by any subjects for whom atovaquone, proguanil, or hypobaric exposure would be contraindicated and to disqualify subjects with mental or physical problems. Female subjects were tested to confirm that they were not pregnant and were advised to take precautions to avoid pregnancy during and up to 3 months after the study. Subjects had to be free of any medication and were asked to maintain regular food and drink patterns during the study period and to take a regular breakfast and lunch on the days when testing took place. Coffee and tea were not allowed in the 6 hours before the assessments. No alcohol was allowed within 24 hours of the assessments in the hypobaric chamber. Subjects were paid for their participation.

**Study Procedures**

Medical examination of the subjects was performed within 7 days before the first study day. The subjects were familiarized with the test procedure and hypobaric environment and were trained on the performance tests. Subjects used the first study treatment for 14 days, followed by a 21-day washout, and subsequently used the second treatment for another 14 days. The study was completed with a follow-up telephone call about possible adverse effects 14 days after the last treatment dose. Medication was administered daily at 6:45 pm, and test sessions were performed in the early evening on days 1 (baseline at 75.2 kPa, without medication), 2, 9, and 16 of each treatment period. Performance testing was conducted in a hypobaric chamber of the Royal Netherlands Air Force, in which the ambient pressure was decreased to 75.2 kPa (564 mm Hg), which equals the lower limit of in-flight cabin pressure of commercial jet airliners.

Subjective assessment of the quality of sleep on treatment days was performed using the Groningen Sleep Quality Scale.23 In addition, subjects had to record the number of awakenings, and their estimated total sleep time during treatment days. On test days 1, 2, 9, and 16, performance and alertness were assessed using the Vigilance and Tracking (VigTrack) task and the Multi-Attribute Task (MAT) battery. These tasks have been identified as the two tasks tapping both sides of the pilot workload spectrum. Both performance tasks have been successfully applied to demonstrate effects of fatigue and sleepiness in pilots.25,26 Sedative effects of alcohol,27 and effects of antihistamines such as triprolidine HCl 5 mg and diphenhydramine 50 mg under conditions of simulated aircraft cabin pressure.20,21 The VigTrack task is a dual task measuring vigilance performance under the continuous load of a compensatory tracking task. The duration of this test is 10 minutes and performance measures include root mean square (RMS) tracking errors, percentage omissions, and number of false reactions.

The MAT battery provides a benchmark set of tasks for use in a wide range of laboratory studies of operator performance and workload. The MAT has been developed by the National Aeronautics and Space Administration (NASA) and Langley Research Center.24,28 The battery incorporates tasks analogous to activities that aircrew perform in flight, while providing a high degree of experimenter control and performance data on each subtask. Features include a system-monitoring task, a tracking task, and a resource management task. The duration of this test is 10 minutes and performance measures include number of false reactions, number of omissions, mean response time, root mean square tracking error, and mean absolute deviation of the fuel target level.

The Stanford Sleepiness Scale (SSS) was used to subjectively assess sedative effects of the study medication.29 Throughout their stay in the hypobaric chamber, the subjects’ oxygen saturation of hemoglobin (SaO2) was recorded using a pulse oximeter with a finger sensor (Nonin 8500M, Nonin). To determine the occurrence of any adverse event, the indirect question, “How do you feel?” was asked before the start of each test session and on each day during both treatment periods; subjects had to report adverse events using a diary.

On test days, subjects stayed for 2 hours in the hypobaric chamber. Each test session included VigTrack, MAT battery, subjective assessment of sleepiness, SaO2 measurement, and assessment of adverse effects. The diary included daily ratings on the Groningen Sleep Quality Scale, recording of sleep characteristics, and recordings of adverse events.

**Data Analysis**

The response over time on flight-related performance was assessed in a within-subjects design. The results obtained with A/P were compared with those observed with placebo. All VigTrack and MAT variables that were repeatedly measured on test days 1, 2, 9, and 16 were tested in separate applications of repeated measures analysis of variance (ANOVA): treatment, group, trial day, treatment × trial day, and full factorial design. When the average test of ANOVA revealed a significant (p < .05) overall difference, univariate F-tests were used to analyze the different contrasts. Paired comparisons between scores within treatment conditions were performed by computing t-tests for paired samples. SSS scores were analyzed by nonparametric statistics (Wilcoxon matched pairs
sign rank test); the Bonferroni method was used to correct for multiple comparisons. Sleep variables were used to test for differences in sleep quality and quantity during the study and were tested in separate applications of repeated measures ANOVA: treatment, trial day, treatment × trial day, full factorial design. All statistical tests were performed at a significance level of $\alpha = .05$.

**Results**

Owing to personal reasons, one subject gave up participation a few hours before the study started; participation of one other subject was terminated after 3 days owing to an upper respiratory tract infection with fever. Unblinding of the treatment assignment showed that this subject was taking placebo. Withdrawn subjects were not replaced, and performance and alertness data were analyzed for the remaining 22 subjects.

**Peripheral Hemoglobin-Oxygen Saturation**

$\text{SaO}_2$ profiles of both treatment conditions did not differ significantly. On test days, mean pretest (sea level) values ranged from 98.4 to 98.7%. $\text{SaO}_2$ values during testing in the hypobaric chamber at 75.2 kPa were significantly lower ($F_{1,21} = 437.63, p < .001$) and ranged from 91.5 to 93.6%.

**Vigilance and Sustained Attention**

Vigilance and sustained attention was tested using the VigTrack task. Results are presented in Table 1. No significant differences between the A/P and placebo conditions were found for RMS tracking errors and percentage omissions. RMS tracking performance improved significantly during the study period for both treatments ($F_{3,63} = 5.81, p < .01$). Vigilance performance (percent omissions) remained stable for both treatment conditions during the study period. No significant differences were found for the numbers of false responses.

**Complex Information Processing**

Complex information processing and resource management was tested with the MAT battery. Results are presented in Table 2. No significant differences were found between the two treatment conditions for mean monitoring response time, RMS tracking error, and mean absolute deviation of the fuel target (resource management). No significant differences were found for the numbers of false reactions or omissions (monitoring).

**Stanford Sleepiness Scale**

No significant difference between A/P and placebo conditions was found for the sleepiness scores. Throughout the treatment period, mean scores ranged from 3.0 to 3.5, corresponding with feelings of being relaxed, awake, not at full alertness, and responsive.

**Sleep Characteristics**

No significant differences were found between A/P and placebo conditions with regard to sleep quality, total sleep time, sleep latency, and number of awakenings during the study period. Mean sleep quality scores varied from 1.0 to 2.6 throughout the study period, indicating that sleep quality was good. Mean total sleep time varied from 7 hours and 13 minutes to 8 hours and 18 minutes, mean sleep latency from 11 to 27 minutes, and mean number of awakenings from 0.5 to 1.6 per night.

**Adverse Events**

No serious adverse events were reported during the study. Adverse events were similar for both treatment conditions and were most frequently related to diarrhea, nausea, sore throat, and abdominal pain (Table 3). Twenty-three subjects reported a total of 17 adverse events while on placebo, and 22 subjects reported a total of 12 adverse events while on A/P. All adverse events were classified as mild (ie, not interfering with normal activities), were short lasting, and disappeared spontaneously. One subject experienced a nosebleed during the trial period and once 14 days after the last trial day. The ear, nose, and throat surgeon diagnosed venous swelling at Kiesselbach’s area, a common cause of nosebleeds in otherwise-healthy people. After cautery, this subject remained free of complaints during a follow-up period of 4 weeks. In follow-up telephone inquiries held 2 weeks after the last trial day, one

### Table 1

**Means (and SDs) of Vigilance and Sustained Attention Variables** on Treatment Days for Atovaquone/Proguanil and Placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 9</th>
<th>Day 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLA</td>
<td>A/P</td>
<td>PLA</td>
<td>A/P</td>
</tr>
<tr>
<td>RMS tracking</td>
<td>10.6 (3.3)</td>
<td>11.0 (3.3)</td>
<td>10.0 (3.3)</td>
<td>10.2 (3.9)</td>
</tr>
<tr>
<td>% omissions</td>
<td>9.4 (8.8)</td>
<td>11.8 (14.7)</td>
<td>10.1 (11.6)</td>
<td>10.7 (14.7)</td>
</tr>
<tr>
<td>No. false reactions</td>
<td>2.5 (3.0)</td>
<td>3.0 (3.8)</td>
<td>2.6 (2.9)</td>
<td>2.1 (2.5)</td>
</tr>
</tbody>
</table>

A/P = atovaquone/proguanil; PLA = placebo; RMS = root mean square.

*Tested using the Vigilance and Tracking task.
subject reported “night sweating” during two nights, but none of the other subjects reported a health complaint.

**Discussion**

The aim of the present study was to investigate the risk of detrimental effects of A/P on flight-related performance under conditions of simulated aircraft cabin pressure. For that purpose, the response over time on flight-related performance was assessed in healthy subjects during 14 days’ treatment with A/P administered once daily. The results of the tests obtained with this medication were compared with those observed with a 14-day placebo treatment. The present study satisfied three important requirements for the aeromedical assessment of the safety of A/P prophylaxis for aircrew:

1. Measurements were performed in a hypobaric environment simulating cabin pressure in commercial airliners.
2. Attention was focused on vigilance, tracking, complex task performance, and sleepiness. Performance measures that were used reflect both sides of the pilot workload spectrum and have shown to be sensitive to detect changes in levels of vigilance and alertness in aircrew.
3. Steady-state blood levels of A/P were anticipated by studying a treatment period of 14 days. The period of 14 days is relevant for aircrew because they often stay for a few days at their tropical destination and have to continue A/P prophylaxis for a week after departure from a malaria-endemic area.

Subjective sleepiness scores are considered to be the inverse representation of levels of alertness. Mean subjective sleepiness scores obtained during the test sessions ranged from 3.0 to 3.5 and indicated that subjects were relaxed, awake, and responsive but not at full alertness. These scores fully compare with mean in-flight sleepiness scores of nonfatigued pilots.25,26 During testing in the hypobaric chamber, mean SaO2 levels were 92.9% in the A/P condition and 92.7% in the placebo condition. These values are comparable to in-flight SaO2 levels found in aircrew and passengers and indicate that the subjects were mildly hypoxic when they were performing the tests under hypobaric conditions.18 Nevertheless, we found no differences in flight-related performance and alertness.
between subjects using A/P or placebo. These results are in conformity with the results of the normobaric study conducted by Paul and colleagues.

Because insomnia, which is a relevant threat to aircrew, is listed as a side effect of A/P in the Dutch pharmacopoeia, we analyzed the sleep variables comparing both treatment conditions. We found no evidence for disadvantageous effects of A/P on sleep quality, total sleep time, or sleep latency. Mean sleep quality scores indicated that sleep quality was good, although one subject reported impaired sleep as an adverse effect while on A/P. The mean total sleep times and sleep latencies that we found were in the range of values that are generally considered normal in the subjects’ age group.

Tolerance of A/P has been investigated in studies well-designed for this purpose. In these studies gastrointestinal problems, diarrhea, and flatulence were the most frequently observed side effects of prophylactic use of A/P. Although the number of subjects in our study was too small to draw firm conclusions about tolerance, it is noteworthy that adverse events rates were similar for A/P and placebo treatment phases (see Table 3). All adverse effects were mild and self-limiting. Diarrhea, nausea, sore throat, and abdominal pain were the most frequently reported effects. Although the profile of adverse effects showed no relevant differences between A/P and placebo, it should be considered that some users of A/P prophylaxis might experience adverse effects. This should be taken into consideration when prescribing A/P prophylaxis to aircrew. They should be informed about the possible effects and made aware of the fact that even uncommon side effects may occur in an individual person. In a case in which side effects might potentially interfere with flight safety, the prophylaxis should be discontinued. This principle applies to all medication prescribed to active aircrew.

Conclusions

In the present study, A/P demonstrated no detrimental effects on alertness and performance on tasks associated with flying in healthy volunteers tested under aircraft cabin pressure conditions. The results indicate that A/P does not impair one’s ability to process information, coordinate complex psychomotor tasks, or sustain attention and vigilance—activities that are vital for maintenance of flight safety. Based on these results and the findings of Paul and colleagues, we conclude that flight performance of aircrew will not be affected by the prophylactic use of A/P during a period of 14 days. Because effective and safe prophylaxis of P. falciparum malaria is important for aircrew flying to malaria-endemic destinations, we recommend aeromedical approval of prophylactic use of A/P by cockpit and cabin crew.

Acknowledgments

We thank Amanda Moerman, physiological training officer of the Royal Netherlands Air Force, for operating the hypobaric chamber; and Lyda Kistemaker, Marieke Pronk, and Koen Tan for coaching the subjects and performing the measurements.

Declaration of Interests

The study was financially supported by GlaxoSmithKline. The authors have no other financial or conflicts of interest to disclose.

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