DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
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AFEB

MAY 21 2004

MEMORANDUM FOR

The Assistant Secretary of Defense (Health Affairs)
The Surgeon General, Department of The Army
The Surgeon General, Department of The Navy
The Surgeon General, Department of The Air Force

SUBJECT: Armed Forces Epidemiological Board (AFEB) Select Subcommittee to Develop Mefloquine Study Options

1. References:

   a. Memorandum, Office of the Assistant Secretary of Defense for Health Affairs/Clinical and Program Policy, March 22, 2004, Armed Forces Epidemiological Board (AFEB) Select Subcommittee to Develop Mefloquine Study Options

2. On April 12, 2004 a select subcommittee of the Armed Forces Epidemiological Board (AFEB) met to provide guidance and make recommendations on the design of a study or studies, directed by the Assistant Secretary of Defense for Health Affairs [ASD(HA)], to address the issue of adverse health effects, including neuropsychological outcomes and suicide, among deployed and recently deployed Service members taking mefloquine. The subcommittee serves in an advisory role only and does not supersede the responsibilities of officials who are responsible and accountable for program management. In addition to the AFEB select subcommittee members, Department of Defense (DoD) and non-DoD experts in malaria, epidemiology, neuropsychiatric disorders, and pharmacology participated in the discussion.

3. The ASD(HA) requested the subcommittee's guidance on the optimal study design or design(s) to address the following research questions:

   a. What are the comparative rates of adverse events (including neuropsychiatric) among deployed Service members using mefloquine, versus doxycycline, or no antimalarial medication?

   b. What are the attributable risk factors (including mefloquine) for suicide among deployed and recently redeployed Service members?

4. The subcommittee was asked to review relevant data sources that could support proposed studies and acknowledge limitations in data collection, particularly in operational theater environments, that could impact the study. The subcommittee was also requested to suggest alternative data sources that could corroborate or strengthen the studies, to recommend proponent agencies for conducting the research, and to consider the most appropriate mechanisms to ensure optimal transparency of study methods and findings.

5. To facilitate the deliberations, before the meeting subcommittee members were provided with a package of published studies on side effects and adverse events associated with antimalarial medications. During the meeting they received a series of briefings that focused on the areas listed below. The presentations are available for review at http://www.ha.osd.mil/afeb

- DoD's historical experience with malaria and malaria prevention measures
- DoD data sources, including personnel assignment information, health encounters, post-deployment assessments, and serum banks
- DoD pharmacy data, including operational settings
- DoD mortality surveillance
- DoD suicide surveillance
- The Millennium Cohort Study

6. The medical literature review demonstrated a considerable body of research regarding adverse events and mefloquine. These include a variety of relatively minor side effects along with rare, serious adverse reactions (e.g. psychoses and seizures). However, few studies have focused on military cohorts, and fewer still have focused on combat operations. There are many reasons to believe that the stressful nature of the high-threat deployment environment might by itself lead to psychological problems, including increased anxiety and depression. Therefore, findings from studies of antimalarial prophylaxis done in other settings might not be directly applicable to the circumstances of deployment.

7. The literature contains reports of suicidal ideation and suicide in persons taking mefloquine. However, no direct relationship between administration of this drug and suicide has been demonstrated. Preliminary review of suicide data through January 2004 among Service members deployed to Operation Iraqi Freedom (OIF) found that mefloquine was present in autopsy specimens in only one of 23 individuals who committed suicide, and only four of these suicides had occurred in units where this drug was prescribed.

8. Suicide has historically been difficult to study objectively. The determination of suicide as a cause of death is not always clear, and multiple and different factors may be associated with this outcome depending on the setting. Any study investigating the potential role of a single factor, such as a specific medication, must take into account a large number of other variables that could confound any potential association.

9. Given the above information and acknowledging the significant obstacles and challenges in conducting the necessary studies, the Board makes the following core recommendations:

(a) **A careful and well-designed descriptive study of the health outcomes potentially related to mefloquine is a pre-requisite to subsequent studies. While side effects such as vivid dreams, nightmares, sleeplessness, headache, and dizziness are of interest, their subjective nature and ease of study in an operational setting make their investigation a lower priority. Instead, efforts should be focused on documenting specific measurable outcomes in the deployment setting. In addition to traditionally evaluated medication-related severe adverse events such as deaths and hospitalizations, deployment-related events including evacuations from theater and lost duty time should be considered, along with other outcomes possibly linked to mefloquine such as criminal violence, attempted suicide, retinal damage, and ototoxicity. In addition to electronically available inpatient and outpatient data, attempts should be made to obtain and assess other sources of adverse events information, including paper-based medical records, theater evacuation records, administrative, and criminal records. These data, once collected, should form the basis for subsequent analytical studies of associations between adverse events and mefloquine use.**

(b) **To assess adverse events associated with mefloquine, the Board recommends either a retrospective, cross-sectional, or prospective cohort study design approach. Cohort studies are preferable because they can assess multiple outcome measures for one or more types of exposures. Given the number of personnel who took mefloquine and other antimalarials in OIF and Operation Enduring Freedom (OEF), a retrospective cohort study may be most feasible. Since the incidence of severe adverse health outcomes is apparently low and recent policy changed the antimalarial of choice to chloroquine in OIF, a prospective study design of mefloquine-related adverse events, while possible, would require years to complete for most outcomes of interest.**

(c) **Because of the rare nature of suicide and the large number of variables that need to be assessed, the Board feels a case-control study design is most appropriate for studying factors associated with suicide, including mefloquine. A carefully constructed case-definition for suicide will be necessary to select cases for inclusion. While the focus should be on current deployments (OIF and OEF), if sufficient data are available, suicides in past deployments could also be captured in this study. The Board recommends considering multiple control groups, including deployed personnel who returned home safely, and personnel who died during deployment for reasons unrelated to suicide. For the case-control study to be valid, controls must be assessed for factors potentially related to suicide to an equal degree as the cases.**

(d) Although military researchers have an outstanding track record in the area of epidemiological and clinical research, in order to ensure transparency and credibility of any planned studies, the Board recommends non-Federal investigators in collaboration with DoD investigators do the studies. Furthermore, an independent non-Federal oversight committee should be established to periodically review the proposed research studies and their findings.

10. Other relevant recommendations include:

(a) A comprehensive review of DoD suicide data should be undertaken. Although extensive investigations are conducted on all fatalities occurring in OIF and OEF, those occurring in other settings are not as thoroughly investigated. In addition, Service-level differences in suicide surveillance and lack of definitive autopsy (including psychiatric autopsy) might result in a skewed and incomplete picture of suicide in the non-deployed setting. Therefore an attempt to more completely describe suicides in the military is warranted. This effort will also help determine an effective control group for the study of suicides in the deployed setting.

(b) To study more common, less severe side effects associated with antimalarials, randomized, double-blinded studies have been successfully conducted. While such studies are generally not feasible in high-tempo operational deployment settings, there may be other opportunities within DoD, such as short-term training exercises requiring antimalarial prophylaxis, where these could be relatively easily conducted.

(c) The Board is aware that within DoD efforts are underway to understand the knowledge, attitudes, and beliefs associated with malaria prevention measures. This undertaking is very important and will be valuable in assessing Service members' relative acceptance of daily versus weekly dosing regimens, and in improving and better targeting malaria educational strategies. To maximize the information derived, the Board suggests it be complemented with a study of malaria prophylaxis compliance using anonymous surveys.

(d) Little is known about unique, individual characteristics associated with severe adverse events associated with mefloquine use. A careful study of this cohort of individuals, including biological and genetic markers, may greatly improve our understanding of these reactions and may help to better target prophylaxis by identifying persons who should not be given certain medications.

(e) Efforts should be made to better document mefloquine use in the operational setting. While the Board commends current activities to document prescribing in-theater, we recognize that current electronic databases alone are probably insufficiently accurate to describe how much and how often mefloquine is being prescribed and dispensed. Alternative data collection methods, such as logbooks and local databases at combat support hospitals and other operational locations need to be explored to minimize misclassification bias. Such efforts, if successful, would also be useful to answer many other questions related to deployment health.

(f) The DoD serum repository may prove useful to better document mefloquine exposure during deployment. Current DoD policy requires the collection of a post-deployment serum sample within 30 days of return. Given the relatively long half-life of mefloquine, it may be possible to use the post-deployment specimens to document exposure to mefloquine and to other anti-malarials.

(g) The Millennium Cohort Study may help in any proposed studies. Standard mental health and psychiatric measures are applied at enrollment; these data may be useful in ruling out pre-existent conditions among those taking part in mefloquine studies. Pre- and post-deployment health assessment questionnaires may also prove useful.

(h) The Board recommends coordinating with the Department of Veterans Affairs (DVA) on any analytical studies conducted. While there is no current evidence that untoward health effects occur months to years after exposure among those not experiencing adverse events while on the medication, veterans may perceive an association. DVA may desire to pursue studies of possible latent effects from the medication and could benefit from the results of DoD studies.

11. The above recommendations and comments were unanimously approved

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