Exposure to quinoline antimalarial drugs: a pre-determinant for neuropsychiatric illness and suicide.

SUBMISSION TO THE SENATE FOREIGN AFFAIRS, DEFENCE AND TRADE REFERENCES COMMITTEE

INQUIRY INTO SUICIDE BY VETERANS AND EX-SERVICE PERSONNEL

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Introduction

The synthetic quinolines are a family of drugs which have been widely used by military forces for prevention and treatment of malaria since the mid-20th century. Members of this family of effective antimalarial compounds have been identified to cause injury to the brain and have been classified as 'neurotoxic'.[1] Two of this family of medications: mefloquine and tafenoquine, were administered to approximately 5,000 Australian Defence Force (ADF) personnel over the last three decades, predominantly in a series of clinical trials conducted by the Army Malaria Institute (AMI) in Bougainville and Timor Leste during the period 1999-2002.[2-7] Although the exact figure is currently unknown, a sizeable minority[8] of these personnel now suffer from chronic neuropsychiatric illness as a result of their exposure to these drugs. Some are known to have suicided (insert Chris Stiles story from paper), while at least several hundred remain at risk of suicide due to the ongoing nature of their brain injury.

Mefloquine

In the ADF, mefloquine has been used for malaria treatment since 1990 and for malaria prevention ("prophylaxis") since 1993, although it was also used in pre-license AMI drug trials during the late 1980s. Initially mefloquine was used as the "second-line" prophylaxis drug after the first line drug doxycycline, but became the third-line drug in 2006 when superseded by malarone as the second line-drug.[10] Specialist ADF personnel such as aircrew and divers have been prohibited from using mefloquine[11] since a 1991 World Health Organisation (WHO) warning regarding the risk of neuropsychiatric side effects.[12]

Although there are no publicly available figures on mefloquine use in the ADF prior to 2001, ADF malaria policy states that 5-10% of personnel do not tolerate the first-drug, doxycycline,[11] which provides a basis for estimates for the 1993-2001 period. From 2001 to 2015 mefloquine was prescribed to at least 659 ADF personnel, in addition to 1,319 personnel administered the drug during AMI clinical trials in Timor Leste in 2001-02.[13] Many personnel serving in East Timor at that time were given mefloquine as a matter of convenience, without having previously taken the safer first-line drug doxycycline and without being properly informed of the risk of neuropsychiatric side effects.

During the early to mid-2000s, the Walter Reed Army Institute for Research (WRAIR), (the organisation that 'discovered' mefloquine as part of a broad screen of bioactive chemicals in the 1970's [1]), published a series of laboratory studies which investigated the potential neurotoxic effects of mefloquine in the brain. Their findings concluded that "*mefloquine's clinical potential may be compromised by neurotoxicity*."[14] Later that year the US Department of Veterans Affairs raised concerns regarding the long-term health impacts of mefloquine use, including the possibility of "*violent and suicidal behaviour, and symptoms similar to post-traumatic stress disorder (PTSD)*" in affected individuals.[15] The WRAIR studies found conclusively in 2006 that mefloquine is neurotoxic, able to cause "*lasting or permanent injury*" to the central nervous system (CNS)[16] linked to the resulting neuropsychiatric symptoms when administered at concentrations equivalent to prophylactic use. The affected parts of the CNS include the brainstem, limbic system and vestibular system, which are linked to balance, hearing, memory, concentration and emotional responses.[1,17]

Mefloquine has long been known to be able to cause severe, adverse neuropsychiatric reactions in a relatively small number of cases, while the drug is in use or shortly thereafter. Due to the broad nature of both neurological, neuropsychiatric symptoms, mefloquine has been suggested to cause a chronic neurotoxicity syndrome[1] incorporating numerous neurological and psychiatric disorders such as insomnia, nightmares, anxiety, depression, personality disorders, suicide ideation, dizziness, vertigo, balance disorders, neuropathies, vestibular disorders, tinnitus and hearing loss, many of which the manufacturer now lists as "common" or "very common" side effects.[18] These reactions can also include seizures, psychoses, hallucinations, violence, self-harm and specifically, suicide and suicidal ideation in both military and civilian travellers. [1-3] [17] Risk factors for an individual to experience a severe neuropsychiatric reaction to mefloquine have been identified and include a history of neuropsychiatric disease [4], being a member of the female sex [5], having no previous exposure to the drug and a low body mass index [6, 7], all of which are factors mentioned in the manufacturer's patient information leaflet [8]. Confounding factors can also include mTBI and PTSD [7, 9-11], both of which are observed in military populations.

The mechanism by which mefloquine causes significant neurological and neuropsychiatric disorders is currently unknown. However, several theories have been suggested which link mefloquine-related neuropsychiatric disease to its cellular mode of action [12-14], or to underlying genetic susceptibility to neuropsychiatric drugs or their binding partners in the brain which are known to be affected in clinical cases of seizures and [15-18].

Tafenoquine

Like mefloquine, tafenoquine is a synthetic quinoline which was initially developed by WRAIR [19], identified during the same program of research that discovered mefloquine. Initially called 'etaquine'[20], the drug was initially tested for the treatment of relapsing vivax malaria, but has subdpsequently been developed for malaria prophylaxis. Tafenoquine has a similarly long elimination half-life to mefloquine, allowing it to also be used as a once weekly rather than daily dose. Tafenoquine, like primaquine its chemical analogue, can cause significant haemolysis in individuals who do not express the enzyme glucose-6-phosphate dehydrogenase (G6PD) and all ADF personnel are screened for their enzymatic profile before being administered primaquine, or in this case, tafenoquine. The only ADF personnel to have been given tafenoquine were approximately 4,000 serving members recruited as subjects in three clinical trials during the late 1990's and early 2000's [21-26]. One of these trials compared the efficacy and safety of tafenoquine to mefloquine among ADF personnel in Timor Leste found that "there was no notable difference" between the incidence or nature of neuropsychiatric side effects in the groups of soldiers given these drugs suggesting the side effect profile of mefloquine and tafenoquine are the same..

Although the research on tafenoquine neurotoxicity is not as extensive as is the case for mefloquine, there is anecdotal evidence that this drug presents a similar risk of chronic illness [27]. Studies have shown that tafenoquine is metabolised to its active form by the liver enzyme cytochrome P450 2D (CYP2D), and that mutation in this enzyme can cause treatment failures with the drug [28]. This may also predispose those with inefficient cytochrome P450 genotype to have potentially toxic levels of the circulating pre-drug due to a failure to metabolise the compound, which may be also related to sex and origin of the patient [19, 29]. CYP2D mutation has also been linked to risk of suicide [30].

Anecdotally, ADF personnel administered tafenoquine during the AMI clinical trials have experienced chronic neuropsychiatric symptoms, including diagnosed psychiatric and neurological disorders, at similar rates to those who were administered mefloquine. Tafenoquine comes from a class of drugs, the 8-aminoquinolines, which have been well known for their neurotoxic properties since the 1940s,[1] and in 2009 WRAIR scientists found that tafenoquine is "more neurotoxic than mefloquine."[23] Tafenoquine has not yet been registered by any national drug regulator, in any jurisdiction, and but is currently in Phase III clinical testing.[22]

Neuropsychiatric Illness and Risk of Suicide in Australian Quinoline Veterans

The toxic effects of mefloquine and tafenoquine have exposed Australian veterans to increased risk of suicide.

In a relatively small number cases this can be as a direct result of an acute psychiatric reaction while the drug is being taken or shortly afterwards, as has been identified in case reports of American and British soldiers exposed to mefloquine [4, 31] or perhaps more commonly from symptoms experienced over a number of years without successful treatment [32]. What is concerning is that many of the neuropsychiatric symptoms caused by the drug, in addition to those neuropsychiatric symptoms such as paranoia, depression and anxiety [33], will present *in addition* to factors known to increase the likelihood of suicide attempt or suicide completion in military personnel such as repeated operational deployment, age, and being a female military member [34-38] .

Due to the complex dependent nature of military deployment, t these factors could also be compounded by concerns about family and friends, issues around employment and housing, and the uncertainty that goes with living as a military family unit with frequent changes of home location. In veterans, in addition to these pre-sensitizing factors, challenges such as relationship breakdowns, unemployment and homelessness, may place the quinoline-affected veterans at the highest risk of suicide.

A second factor which complicates the diagnosis and treatment of mefloquine veterans is that many of the drug's chronic psychiatric side effects are similar to the symptoms of other disorders such as personality disorders or PTSD [11, 32]. Several health authorities and research institutions have recognised that mefloquine use can confound the diagnosis of PTSD.[21] A large proportion of Australian veterans who have sought medical help for the effects of mefloquine toxicity have been diagnosed and treated for PTSD.

In some cases these diagnoses have occurred without the veteran meeting the appropriate diagnostic criteria. Incorrect diagnosis is a cause for concern because some of the treatments for these disorders including neuroactive medications or electro-convulsive therapy (ECT) can be harmful to patients with brain injuries. The symptoms experienced by those who have suffered an adverse reaction to mefloquine exposure are commonly unresponsive to the usual pharmacological interventions, or psychotherapy approaches used to treat neuropsychiatric disorders in veterans [32]. This factor commonly results in the sufferer receiving multiple or long-term pharmacological interventions [32, 39, 40], or moving between treatments programs with little or no improvement.

The difficulties experienced by many affected veterans in receiving appropriate diagnosis and rehabilitation for acquired brain injury (ABI), as opposed to "mental health" disorders, has further contributed to self-harm and suicidal behaviour in many cases. Given the lack of awareness of quinoline toxicity among health professionals, quinoline veterans who do seek help are typically diagnosed with mental health disorders without proper investigation or differential diagnosis of chronic CNS toxicity.

Without proper diagnosis these veterans have then not fully responded to these treatments, leading them to be described as "treatment resistant". Unfortunately, many of these treatments are not only ineffective but can also be dangerous, placing the affected veterans at further risk of harm including suicide.

Conclusions

- Adverse events resulting from ingestion of the antimalarial treatment mefloquine can increase the risk of suicidal ideation, suicide attempt and completed suicide in a proportion of those that take it.
- Service as a member of a military unit increases the risk of suicide under certain conditions, which can then be further increased by exposure to mefloquine during deployment.
- Exposure to the quinoline family of antimalarial drugs, specifically mefloquine and tafenoquine, has undoubtedly significantly impacted the quality of life of a significant number of ADF veterans who took them, and in some cases resulted in both attempted and completed suicide.
- Acknowledgement of the health impacts of these drugs has, in part, been acknowledged by the Department of Defence, but action to mitigate these effects and improve the health of those affected has yet to be effectively implemented.
- The current information presented by Defence does not acknowledge the risk of veteran suicide associated with mefloquine (and possibly tafenoquine) exposure, this shortfall needs to be addressed in their published information sources.
- Immediate action needs to be taken to provide better healthcare for those impacted by exposure to quinoline antimalarials during their military service, to provide treatment and / or rehabilitation for their injury, and reduce the risk of suicide in this population.

Recommendations

The nature of quinoline toxicity and its health impacts necessitates a dedicated outreach program for affected veterans, families and health professionals. An outreach program by the Departments of Defence and Veterans Affairs was first proposed more than two years ago and has been the subject of discussion with both departments on numerous occasions since that time.

The Committee's previous inquiry into the mental health of ADF personnel and veterans supported the implementation of such an outreach program, recommending that the Department of Defence contact affected veterans and provide them with appropriate health screening.[24] Given the risk factors associated with certain CYP450 genetic types, screening

for CYP2D6 allelic variation could also be undertaken to inform likelihood of adverse drug reactions to the quinoline antimalarials, and also best practice for pharmacalogical intervention, when necessary. The Department of Veterans Affairs should be the lead agency in establishing the quinoline veterans outreach program. In order to achieve this, the Department should convene a group, at the earliest opportunity, of appropriate health professionals, including psychologists, psychiatrists, neurotoxicologists, rehabilitation and ABI specialists and veteran community representatives, to develop clinical guidelines for diagnosis and management of affected past and serving veterans and establish models for rehabilitation and treatment. This model would also provide the basis for a program of awareness and training for health professionals involved in veterans' health care Australia-wide.

Non-liability health care should be offered to all veterans exposed to the drugs and experiencing the acute or chronic symptoms, while the Repatriation Medical Authority (RMA) develop a Statement of Operating Principles (SOP) for ABI to facilitate disability claims.

Staff of the Veterans and Veterans Families Counselling Service (VVCS) should undergo training in recognition of the clinical presentation of quinoline adverse reactions, and ABI, allowing counsellors to provide improved support to those affected, as is the case with other prevalent illnesses such as PTSD.

Delivery of appropriate health care for veterans affected by quinoline toxicity could be provided by specialist ABI health care providers, which are available throughout Australia.

Concurrent with this outreach program there is an urgent need for research to better understand the toxicity of mefloquine and tafenoquine, the resulting chronic health impacts, improved diagnostics and rehabilitation. This research should include follow-up health studies for veterans who were administered these drugs, laboratory toxicity studies, pharmacogenetic studies to determine susceptibility to the drug toxicity, and efficacy of appropriate treatment and rehabilitation methods.

The implementation of this proposed outreach program, and pharmacogenetics testing for all current ADF members prior to antimalarial prescription, as well as further research into the presentation and treatment of these clinical syndromes, should be an integral part of the Commonwealth's efforts to reduce the rate of serving and past ADF veteran suicide in Australia.

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