Malaria, Mefloquine and the ADF

Brigadier Leonard Brennan
Director General Strategic Health Coordination/
Director General Army Health Services
Disclaimer

• Prescriber of mefloquine since 1993
• Volunteer for AMI Clinical Trials in Bougainville (Tafenoquine and Malarone)
• Investigator in Tafenoquine / Mefloquine trial in Timor Leste 2000-01
• As Director Military Medicine 2015 had responsibility for ADF health policy
• Current role have responsibility for AMI
Defence Force accused of 'massive cover-up' over anti-malarial drug
Scope

- Malaria and the ADF
- Anti-malarials
  - Mefloquine
  - Tafenoquine
- The concerns
  - The trials
  - Perceptions vs reality
- Defence response
- Managing individuals who present with concerns
Disease of military significance
Stopped the ADF 3 Times!

• 1918 Palestine
  – 3 cavalry divisions stopped 2 weeks into offensive against Turkish forces

• 1942-3 New Guinea
  – Operations ceased from disease rates > 1% / day:
    – hospitalizations 0.3% / day

• 1968 Vietnam
  – drug resistant malaria epidemic caused 17% casualties in infantry soldiers
The Australian Army Malaria Institute (AMI)

• A world leader, regional WHO collaborating centre

• Roles
  – research infectious diseases pertinent to ADF in Areas of Operation
  – investigate measures to prevent catastrophic mission failure due to infectious diseases.

• Research includes prevention & treatment of vector-borne disease through:
  – pharmacological agents
  – physical means
Force Protection
Defence in depth

• Risk assessment
• Prevention of infection
  – Education
  – Bed nets, long sleeves, impregnated uniforms, repellant
  – Fogging
• Prevention of illness
  – Prophylaxis
  – Eradication
• Treatment
Anti-malarials

Post 80s

• Pre-90s – Chloroquine, Maloprim Fansidar
• Wide spread chloroquine and anti-folate resistant falciparum in region in mid 80s
• Doxycycline 100mg daily – first line
• Mefloquine 250 mg weekly
  – second line until 2006
  – now 3rd line (aka “drug of last resort”)
• Malarone (Atovaquone 250 mg + proguanil 100mg/day) - second line post 2006
• Eradication: Primaquine twice daily for 14 days
Why Doxycycline?

• Effective – e.g. in Cambodia and Somalia
• Mefloquine resistance on Thai/Cambodia border
• Concerned re adverse effects
  – Mefloquine had neurotoxic effects (at the time thought to be 1:1300 to 1:1500)
• Mefloquine cannot be used in:
  – Past history of epilepsy, psychiatric disorders
  – Aircrew
• Added benefits - acne
Mefloquine

- Registered in Australia as an anti-malarial since 1988; for prophylaxis since 1993
- First used along with doxycycline in ADF 1989
- Perhaps the most commonly used anti-malarial in the world ~35 million
- Recommended by many travel clinics for civilians
- Neuropsychiatric side effects are known but in most resolve when cease medication
- Emerging evidence of persistence of side effects in some individuals – mimic other conditions (e.g. PTSD)
- Past history of neurospsych issues a contraindication
<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Not known</th>
<th>Agranulocytosis, aplastic anaemia, leukopenia, leukocytosis, thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Not known</td>
<td>Decreased appetite</td>
</tr>
</tbody>
</table>

### Psychiatric disorders

<table>
<thead>
<tr>
<th>Very common</th>
<th>Abnormal dreams, insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anxiety, depression</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania, paranoia, suicidal ideation</td>
</tr>
</tbody>
</table>

### Nervous system disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>Dizziness, headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not known</th>
<th>Cardiovascular disorders (hypotension, hypertension, flushing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Dyspnoea, pneumonitis of possible allergic etiology</td>
</tr>
</tbody>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Not known</th>
<th>Nausea, diarrhoea, abdominal pain, vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Dyspepsia</td>
</tr>
</tbody>
</table>

### Hepatobiliary disorders

| Not known | Drug-related hepatic disorders from asymptomatic transient transaminase increase to hepatic failure |

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Rash, erythema, urticaria, alopecia, hyperhidrosis, erythema multiforme, Stevens-Johnson syndrome</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorders

| Not known | Muscular weakness, muscle spasms, myalgia, arthralgia |

### General disorders and administration site disorders

| Not known | Oedema, asthenia, malaise, fatigue, chills, pyrexia, hyperhidrosis |

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**Very common (≥1/10)**

**Common (≥1/100 to <1/10)**

**Uncommon (≥1/1,000 to <1/100)**

**Rare (≥1/10,000 to <1/1,000)**

**Very rare (<1/10,000)**

**Not known (cannot be estimated)**
Mefloquine in Aircrew

- Doxy or Malarone – 2 day ground trial
- Mefloquine never authorised in the ADF due to
  - sudden onset of neuropsychiatric side effects
  - fine coordination
  - spatial discrimination
- TMUFF for 4 weeks if taken IAW policy
Mefloquine in the ADF

- Two trials – 1319 ADF members
- 2000 to end June 2016: 669 other ADF pers prescribed mefloquine outside of trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Mefloquine</th>
<th>Malarone</th>
<th>Doxy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>25</td>
<td>105</td>
<td>3536</td>
</tr>
<tr>
<td>2011</td>
<td>26</td>
<td>100</td>
<td>4721</td>
</tr>
<tr>
<td>2012</td>
<td>13</td>
<td>152</td>
<td>7313</td>
</tr>
<tr>
<td>2013</td>
<td>20</td>
<td>187</td>
<td>6436</td>
</tr>
<tr>
<td>2014</td>
<td>35</td>
<td>183</td>
<td>5954</td>
</tr>
<tr>
<td>2015</td>
<td>18</td>
<td>101</td>
<td>5951</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Mefloquine</th>
<th>Malarone</th>
<th>Doxy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>11,654</td>
<td>8,418</td>
<td>847,607</td>
</tr>
<tr>
<td>2006</td>
<td>12,401</td>
<td>10,418</td>
<td>830,333</td>
</tr>
<tr>
<td>2007</td>
<td>15,572</td>
<td>23,278</td>
<td>959,859</td>
</tr>
<tr>
<td>2008</td>
<td>16,033</td>
<td>24,953</td>
<td>986,983</td>
</tr>
<tr>
<td>2009</td>
<td>13,324</td>
<td>25,841</td>
<td>916,281</td>
</tr>
<tr>
<td>2010</td>
<td>14,393</td>
<td>29,287</td>
<td>935,312</td>
</tr>
</tbody>
</table>

Total = 1907
Tafenoquine

- A new once a week anti-malarial related to primaquine
- Studies in >4000 personnel shows promise in terms of side effects & effectiveness
- No recorded neuropsychiatric side effects
- Uncommon - vortex keratopathy (deposits on cornea)
- Tested by the ADF for prophylaxis, eradication and treatment in late 90s, early 00s
- Current status: granted Breakthrough Therapy designation by the FDA in Dec 2013
### Tafenoquine Use

<table>
<thead>
<tr>
<th>Years</th>
<th>Location</th>
<th>Use</th>
<th>Tested against</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998-9</td>
<td>Bougainville</td>
<td>Eradication post deployment (3 days)</td>
<td>Primaquine (14 days)</td>
<td>378</td>
</tr>
<tr>
<td>2000</td>
<td>Timor Leste</td>
<td></td>
<td></td>
<td>639</td>
</tr>
<tr>
<td>2000-1</td>
<td>Timor Leste</td>
<td>Prophylaxis</td>
<td>Mefloquine</td>
<td>492</td>
</tr>
<tr>
<td>2000-1</td>
<td>Australia</td>
<td>Treatment of relapsing malaria</td>
<td>Nil</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1540</td>
</tr>
</tbody>
</table>

- Not registered with the TGA but:
  - trials legal if cleared by ethics committee
    - cleared by ADHREC
  - TGA Special Access given for the treatment trial
So why the focus on ADF?

- Overseas militaries use it less conservatively but reflects on ADF
  - Used as first line, handed out without prescription/consultation
- Anecdotally associated with suicides in the US military
  - Temporary ban by SF
- Concerted media campaign – international to local focus
- Military deployments are high risk in general
  - Trauma, stress – physical and mental
  - Cohort of veterans with chronic mental health issues
- Broader issue: mistrust, lack of understanding of DVA
- Perceptions around trials
Claims/ Misperceptions

• “100s” of people with chronic effects/ “mefloquine toxicity”/acquired brain injury secondary to MQ

• Perceptions around trials*
  – Secret trials
  – “guinea pigs”
  – not voluntary (“do trial or don’t deploy”)

• Soldiers don’t report symptoms – fear career effects

• Tafenoquine also causing chronic symptoms

Chronic Effects
From Product Information

• Due to the long half-life of LARIAM, adverse reactions to LARIAM may occur or persist up to several weeks after the last dose.

• In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the medicine.

• There have been rare reports of suicidal ideations. No relationship to drug administration has been established.
• 63 soldiers developed malaria on doxycycline during INTERFET
  – compliance issues with daily dose?
  – development of doxy resistance?
• Mefloquine was approved, could be given weekly and was in common use by allies
• Two prophylaxis trials conducted by AMI from 2000 – 2002:
  – Tafenoquine vs mefloquine
  – mefloquine vs doxycycline
Ethics and Consent

• Trial cleared by the Australian Defence Human Research Ethics Committee (ADHREC)
• Risks identified in information sheet/consent form
• Informed consent

VOLUNTARY PARTICIPATION
Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. You may withdraw from the study at any time without detriment, but if you choose to leave the study you should advise the study investigators. Should you not wish to participate in the study, you will receive the normal antimalarial course of Doxycycline daily and an eradication course of Primaquine and will still have all the required blood samples taken for redeployment and post deployment screening.
Trial Outcomes

- Not “secret” - results of trials published in scientific literature
- Similar rate of side effects overall
  - 3 serious adverse events on MQ vs doxy trial
    - 2 had undeclared pre-existing problems
  - No SAE on TQ vs MQ
    - corneal effects but all resolved
- >93% would take mefloquine again
- Surveillance during, at the end of trial, then in routine ADF health surveillance
- Doxycycline & mefloquine (and TQ) equally effective - mefloquine remained second line
What has Defence done?

- Transparency and truth
- Communications – seek assistance  
  - GPs, DVA
- Clinical Guidelines for ADF Mos
- Contact address: ADF.Malaria@defence.gov.au
- Public Health forum in Townsville
- Meetings with ex-service organisations
Is there an epidemic?

- Review of ADF suicide database from 2000 – no individuals identified as taking mefloquine
- Review of Medical Employment Classification outcomes between the study groups*:
  - no significant difference in fitness for service
  - no significant difference in PTSD diagnosis
- No evidence of an epidemic
- Stigma related to mental health conditions may be a factor

* overall, doxy vs mefloquine; tafenoquine vs mefloquine
Literature Review

• Side effects were known early, but continuation of effects after stopping is a more recent concern
• Various theories on how mefloquine might cause neuropsychiatric effects
• Varying conclusions about potential toxicity
• No specific way to diagnose chronic mefloquine effects - symptoms shared with conditions such as PTSD
• No specific treatment except to treat the symptoms (and cease the drug when symptoms develop)
  – the underlying symptomatic disorder should be treated as is the general practice of psychiatry
Approach for GPs

- History and document symptoms
  - If no symptoms while on MQ, OR symptoms ceased when medication ceased then it is very unlikely that current symptoms caused by MQ.
Approach for GPs

- History and document symptoms
- Examination, including audiogram, Sharpened Romberg
- Psychological screens
  - K-10, DASS-21, DAR or CAPS-5.
- Further diagnostic investigations, specialist referral as appropriate
  - Neurologist; Neuropsych; Psychiatrist
- Be sympathetic – understand broader context
  - “moral injury”?

Clinical Guidelines for providing appropriate care to ADF members concerned about having been prescribed Mefloquine

PURPOSE
These clinical guidelines are primarily designed to assist clinicians manage patients who are concerned about having been prescribed mefloquine and specifically those that are suffering from neuropsychiatric symptoms which they attribute to historical use of mefloquine. They may also be useful in managing any patients with neuropsychiatric symptoms attributed to other medications or of unknown cause.

BACKGROUND
There has been much publicity in the civilian media and concern raised by some serving and ex-serving ADF members relating to the use of mefloquine for chemoprophylaxis by the Australian Defence Force. The United Kingdom is experiencing similar concerns and the United States has experienced similar concerns in the past.

On 30 November 2015, Defence released a statement on the use of mefloquine in the ADF that advised if “any ADF member, past or present is concerned that they might be suffering side-effects from the use of mefloquine Defence encourages them to discuss their concerns with a medical practitioner so they may receive a proper diagnosis and treatment.”


It is anticipated that Defence medical officers will encounter ADF members who are concerned that they may be suffering side-effects from historical use of mefloquine.

Mefloquine side-effects
Mefloquine has been registered for malaria chemoprophylaxis in Australia since 1993, and has been prescribed to over 30 million people worldwide. The side-effects
DVA Services

- Post discharge GP assessment
- Non-liability health care
- Veterans and Veterans Counselling Service
- Special processing team
- Recognised in several Repatriation Medical Authority Statements of Principles
  - Depression, suicide
- Mefloquine web page

Our messages

• Seek treatment and help regardless of the cause
  – as early as possible but it's never too late
• If treatment hasn’t worked don’t give up
  – some treatments work for some and not others
  – sometimes it takes more than one approach
• Consider non-liability health care
• Put in your DVA claim
• If you’re not happy with treatment
  – Talk to your doctor
  – Contact JHC: adf.malaria@defence.gov.au