Healthy people need safe drugs too: lessons from Lariam and Halfan

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Introduction
Lariam (mefloquine) is an antimalaria drug discovered by the US Army shortly after the Vietnam War, and subsequently marketed worldwide by F. Hoffmann-La Roche. The first reported trials of mefloquine were in prisoners, and were performed at the Joliet Correctional Center, Illinois, in 1975, and at the Maryland House of Correction in 1976. 1, 2

Halfan (halofantrine) is an antimalaria drug chemically related to mefloquine and quinine. Like Lariam, Halfan emerged from the US Army’s huge post-Vietnam antimalaria drug discovery programme. Halfan was first described in the literature in November 1982. 3 During the 1980s and 1990s, Halfan was marketed by SmithKline Beecham.

Lariam and Halfan were intended primarily as drugs for healthy people, to prevent them from acquiring malaria. There is no question that safe and effective antimalaria drugs were urgently needed at the time, since it was plain that the malaria parasite had developed resistance to chloroquine: this phenomenon was observed first in Thailand in 1957, then on the Colombian-Venezuelan border in 1959, and in Kenya and Tanzania in 1978. 4 Within a decade of their being marketed, however, the safety of both these novel agents was in doubt.

Andrew Herxheimer and others investigated some of the concerns around Lariam and Halfan. A Cochrane systematic review identified importance gaps in the Lariam knowledge base, some of which have now been filled. 5 Halfan no longer appears in the BNF. 6 Lariam however continues to be widely prescribed, against a background of persisting controversy, and to date has been given as malaria prophylaxis to over 24 million travellers worldwide. 7

This paper will look at the unusual developmental history of these two antimalaria agents, explain the circumstances under which both drugs fell into disfavour with consumers, and summarise the lessons we should learn to prevent a repetition of the same mistakes.
Background
Both Lariam and Halfan were discovered at the Experimental Therapeutics Division of the Walter Reed Army Institute of Research (WRAIR), in Washington D.C. In the earliest published reports, these two drugs had not yet been named, and they were still referred to by their respective Walter Reed experimental numbers, as “WR 142,490” and “WR 171,669”\(^1,3\). Lariam and Halfan were the two main progeny of the WRAIR malaria drug discovery programme, which ran from 1963 until 1976.

Over a fifteen-year period, vast resources were voted by the US federal government to fund WRAIR’s antimalaria drug research, which at the time was the largest drug discovery programme ever mounted. Because of the size and urgency of the task, WRAIR collaborated with numerous governmental, academic and commercial organisations, including 175 external contractors.\(^8\)

The clinical challenges presented by the Vietnam War (when at one stage 1% of US combat troops were succumbing to malaria each day) were still fresh in the minds of voters.\(^9\) US politicians of the Johnson, Nixon and Carter eras were determined that malaria would never again pose a threat to US expeditionary forces.\(^9\)

From the early 1960s onwards, WRAIR screened over a quarter of a million potential antimalaria compounds.\(^10\) Lariam was number 142,290 in this long series, and Halfan was number 171,669. Because the US military was and remains forbidden by Congress from pursuing any commercial activity, WRAIR engaged Hoffmann-La Roche and SmithKline Beecham to market these two drugs.

The precise details of the three-way business agreement between WRAIR, the US federal government, and the two multinational drug companies which marketed Lariam and Halfan have not been made public. It appears however that all of WRAIR’s phase I and phase II clinical trial data on Lariam and Halfan were handed over to Hoffmann-La Roche and SmithKline Beecham, gratis. This of course greatly reduced the developmental costs to the two drug companies of the two novel antimalaria agents, making them a commercially attractive proposition.

The US federal government then seems to have used its influence in support of Hoffmann-La Roche and SmithKline Beecham, at the point when the US subsidiary of each company came to file a New Drug Application with the Division of Anti-infective Drug Products of the Food and Drug Administration (FDA). Lariam was approved by the FDA in 1989, for marketing in the USA. Halfan was similarly approved in 1992.

From the perspective of the two drug companies chosen to act as the marketing arm of WRAIR, the primary commercial potential of Lariam and Halfan lay in their ability to prevent malaria in tourists and business travellers to the tropics. Prior to their being licensed by the FDA, however, no pivotal Phase III study was carried out on either drug, in a mixed population of general travellers.\(^11\) Likewise, there was no attempt prior to licensing to explore the likely drug-drug interactions of either Lariam and Halfan; some of the fatal drug
reactions which followed may have been a direct consequence of this dangerous gap in the prescribers’ knowledge base.

Within months of their being licensed, major safety concerns around Lariam and Halfan began to emerge. These two drugs, which should have been seen as safe, effective and lifesaving, were viewed by consumers with growing alarm.

The situation today
Though still prescribed in most countries, both for preventing and treating malaria, Lariam has acquired a worldwide reputation for causing neuropsychiatric adverse effects. This unexpected property was confirmed by three recent multicentre randomised controlled trials, all of which found an excess of neuropsychiatric adverse effects in the mefloquine arm. As a prophylactic agent, Lariam is now unpopular with travellers, and especially with young travellers. It has been associated with 18 deaths in travellers and other users (Table).

Table. Deaths associated with the use of Lariam (mefloquine)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient nationality</th>
<th>Patient age</th>
<th>Clinical details</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>USA</td>
<td>Not stated</td>
<td>After one mefloquine tablet – cardiopulmonary arrest, death.</td>
</tr>
<tr>
<td>17</td>
<td>Thai</td>
<td>13</td>
<td>Recrudesced 21 days after mefloquine treatment. Given halofantrine over 3 days – sudden cardiac arrest, death.</td>
</tr>
<tr>
<td>18</td>
<td>British</td>
<td>6</td>
<td>Developed blistering of lips and oral mucosae. Generalised erythema / blistering, then exfoliation of mucosae. Ulceration of mucosae, hair / nail loss. Cardiac asystole, death.</td>
</tr>
<tr>
<td>19</td>
<td>British</td>
<td>37</td>
<td>After taking mefloquine for overseas trip – acutely depressed. Committed suicide by jumping to his death from roof of a mansion block.</td>
</tr>
<tr>
<td>21</td>
<td>USA</td>
<td>22</td>
<td>Early during mefloquine prophylaxis – fever (102 degrees), chills, headache, cough. Treated as &quot;malaria&quot;. Then 2-hour car ride, &quot;head rush&quot;, collapsed, died.</td>
</tr>
<tr>
<td>22</td>
<td>British</td>
<td>Not stated</td>
<td>Eight fatal reactions to mefloquine, reported to the UK Medicines Control Agency.</td>
</tr>
<tr>
<td>23</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Four fatal reactions to Lariam, held on the manufacturer’s database of adverse drug reactions.</td>
</tr>
</tbody>
</table>

Also unexpectedly, Halfan was found after licensing to cause ventricular dysrhythmias that were often fatal. Halfan is no longer recommended by WHO for self-treatment of malaria, and it has been quietly dropped from the
pharmacopoeias of most countries. It is not now approved in any country for malaria prophylaxis.

The disappointing performance in clinical practice of these two drugs, developed at vast cost to the US taxpayer, could not have been foreseen 30 years ago. Or could it?

What went wrong?
Both Lariam and Halfan are products of what has been called “the military-industrial complex”. This is an overused term, but it describes a real entity. The partnership between industry and the military has achieved some astonishing technical feats, like placing a man on the moon. In the area of patient care, however, the health and wellbeing of consumers of healthcare is protected by regulations which, however imperfect and seemingly cumbersome, are derived from decades of use and experience. These regulations reach out into the future, protecting future cohorts of patients from prescriber-induced harm, but also slowing up pharmaceutical innovations which in some cases may be needed urgently. Powerful lobbies, impatient of delay (and acting in what they may see as the public’s best interests) may be tempted to disregard those regulations. However they do so at their peril.

As stated above, the pivotal safety and pharmacokinetic studies which should have been performed prior to the licensing of Lariam and Halfan, on the main intended target group for both drugs (namely, tourists and business travellers), were never carried out.

In the case of Lariam, the first randomised controlled trial of the drug in a mixed population of general travellers was not performed until 2001. Of the study participants randomised to receive mefloquine, 67.1% reported ≥1 adverse event, and in 6% of mefloquine users these events were severe (defined as requiring medical advice). Had this knowledge been available, as it should have been, prior to licensing, then it is certain that the FDA and the other national licensing authorities that approved Lariam for use prophylactically, in and around 1989, would not at the time have endorsed this drug.

It seems more likely than not that in the late 1980s and early 1990s the FDA and other national licensing bodies were influenced, perhaps subliminally, by the powerful military-industrial-governmental lobby into over-hasty decisions to approve the marketing of both Lariam and Halfan. These two drugs were authorised for use on the basis of a very incomplete knowledge base, and at too early a stage in the normal cycle of drug development.

Post-marketing surveillance of Lariam and Halfan proved inadequate, as is so often the case.

Travel medicine experts in most countries were slow to pick up the danger signals associated with these two drugs, and for many years the public’s concern about Lariam, in particular, was dismissed as “media hype”. A senior WRAIR scientist, writing as late as 2001, deplored what he called “...the ‘herd mentality’ of mefloquine associated psychoses”, and stated defiantly that “mefloquine (Lariam®) remains the prophylaxis of choice for US soldiers and travellers.”
As recently as 2005 a reviewer in the New England Journal of Medicine, also an employee of the US military for over 20 years, continued to maintain, in the face of recent and compelling experimental evidence proving the exact opposite, that Lariam is a “well tolerated” drug.29

The victims of this pharmacological muddle have been those many business travellers, tourists, aid workers, missionaries and others who were well at the start of their journeys into malaria-endemic areas, were prescribed Lariam or Halfan by their physicians, and who then suffered unforeseen harms (unforeseen because unresearched) from their chemoprophylaxis. Effectively, all users of Lariam and Halfan, from the point of licensing onwards, have been involved in a natural experiment to determine the true safety in practice of these two antimalaria drugs. They have been unwitting recruits in this hazardous study, however, rather than informed partners.30,31 The rapid public rejection of Lariam and Halfan could have been anticipated, given that users of malaria chemoprophylaxis differ from normal patients in that they are by definition healthy people, and quite reasonably they are unwilling therefore to accept even relatively minor drug-related harms.32,33

Ironically, for a drug that was discovered by the military, soldiers have been amongst the most vocal critics of Lariam. Following a Parliamentary enquiry, Canada’s auditor general condemned protocol abuses in which 900 Canadian soldiers deploying to Somalia were prescribed Lariam in 1992-1993, at a time when mefloquine was still unlicensed in Canada.34 In the US, military epidemiologists investigated the possible role of Lariam in a series of murders and suicides among soldiers in North Carolina who had served in Afghanistan.35 Most recently, the Australian military has been threatened with legal action by soldiers reporting severe and disabling symptoms which they attributed to Lariam.36

The future
The prime lesson from the Lariam and Halfan debacle is that drugs intended primarily for use by healthy people must be genuinely well tolerated, and indeed they must demonstrate much better tolerability under the actual conditions of use than would normally be required for, say, antimitotic agents.37

Despite the public outcry about Lariam and Halfan, it is extraordinary that no real attempt has been made to explore the adverse effects of Lariam and Halfan in terms of what causes these effects, who is likely to experience them, how long the effects normally last, how the effects can be lessened, and how they should be treated if they do occur. In 2002 Croft and Herxheimer published a critical review of 516 published case reports of Lariam adverse effects, and suggested that many of these effects are a post-hepatic syndrome caused by primary liver damage with, in some users, symptomatic thyroid disturbance; however, the study which the authors proposed for testing their hypothesis has not been carried out.38

Because the harms of Lariam have never been adequately investigated, and because there appears to be no incentive for the manufacturer of Lariam ever to do this, it is likely that Lariam, which like Halfan is a potentially important weapon in the limited pharmaceutical arsenal against malaria, will be discarded
along with its sister drug. This represents a waste of resources, and a loss also to future travellers and patients. We must learn from this experience or be condemned to repeat it. Many of the medical tragedies detailed in the table need never have occurred. Powerful institutional pressures must never again override the needs and rights of patients.

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References


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