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FLY IN THE OINTMENT

It has been accused of bringing on psychosis, fits and hallucinations. Some say it can kill. Are the side effects of the latest anti-malarial drug worse than having the disease itself? By Lynn Eaton

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The tablets were large and white and seemed innocuous enough. Helen Whitehead took the first one 10 days before she was due to fly out on what should have been the holiday of her life. She had just left Newcastle University with a degree in social studies, and the eight-week trip to Africa was a graduation graduation gift from her mother. Whitehead, an outgoing 25-year old, felt emotional and "clingy" after taking the antimalarial tablet Lariam. It was uncharacteristic, but she put it down to preflight nerves and took the second pill three days before departure, as prescribed. This time there was no mistaking her anxiety. She could not sleep; nerves, not excitement, were keeping her awake. By the time she touched down in Zambia she had not

slept for two days and was jet-lagged. Normal, then, to feel disturbed by such a different environment from safe old England, she thought. "It was a completely different culture. I had never been anywhere like that before, with lots of guards carrying guns."

She expected to adapt to the strangeness of her surroundings. Instead she became daily more alienated, her thoughts increasingly bizarre. She sensed an "evil" presence in her host's house and was convinced she was about to be drugged or kidnapped. "I thought people were trying to put a curse on me," she says. She heard messages from the television telling her to live on another planet. "I remember thinking it

was the end of the world. I was just scared, really scared."

In clinical terms, Whitehead was psychotic within days of leaving Britain. Dr Cindy Buckley, a GP specialising in repatriation, flew out to Lusaka to fetch her home. "Helen wasn't the first case I had heard of. I already knew of one person who had had a fit. Since then I have brought back one other person like Helen. We are not talking about people being a little bit agitated or anxious. They were psychotic."

Whitehead recalls the flight home clearly: "I remember thinking when we went into an air pocket, I have got to keep it together or the plane is going to

crash. And I thought when I got home there would be loads of press waiting because I had been kidnapped.”

The small print on the information sheet in Whitehead's pack of Lariam warned that it could cause neuro-psychiatric reactions, such as panic attacks. The drug is not recommended for people with “a history of psychiatric disturbances”. Whitehead had no such history, yet her symptoms were far worse than the average panic attack.

She came off antipsychotic drugs after a week but continued to feel dizzy, with memory loss. Her concentration was too poor to watch television. “I was paranoid, couldn't go out, and felt very vulnerable and threatened.” Three years after her holiday in Zambia, she still experiences chronic fatigue and anxiety and is unable to work. Her career is what might politely be termed “on hold”. Worried that her episode of psychosis might affect her job prospects, she obtained a private psychiatric report from Dr Michael Lough of the Cleveland Nuffield Hospital in Stockton-on-Tees. He dismissed jet lag, fatigue and emotional trauma as causing her illness and concluded categorically: “The psychiatric disorder that the plaintiff suffered was a consequence of her ingestion of Lariam.”

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The British make an estimated 42m visits abroad each year. Many have jabs or take drugs as a matter of course to reduce the risk of disease in certain countries. Few stop to consider whether the risk of side effects might outweigh the potential benefits.

Yet Helen Whitehead is not alone in experiencing a serious reaction to Lariam that she says has blighted her life. Since it was developed as an antimalarial alternative for destinations where there is a growing resistance to more established drugs, other users have also become seriously ill, apparently as a result of Lariam. They have suffered epileptic attacks, severe depression, hallucination and temporary insanity. Lariam has also been cited as a factor in an acute skin reaction that led to the death of a six-year-old girl, and in the suicide of a 37-year-old barrister who had taken the drug during a trip to east Africa.

Whitehead is one of 46 British people to have issued writs against the drug's manufacturer, Hoffmann-La Roche. A further 150 are in the process of doing so, half of them funded by legal aid. Another 500 people have contacted the lawyers leading the action. They claim that under the 1987 Consumer Protection Act, Roche marketed a defective product and failed to give adequate warning of the side effects. In America, lawyers lodged their first case against Roche in January, on behalf of a 25-year-old Californian who says he has suffered Lariam side effects for two-and-a-half years.

Roche has always maintained that the overall incidence of side effects with Lariam — including minor irritations such as nausea — is comparable with that for other antimalarial drugs. A spokesman said: “Roche has always provided health professionals and travellers with appropriate information on the possible side effects:”

Weighing up acceptable side effects against a potential killer like malaria is fraught with complications. An estimated 3m people worldwide die each year after being infected with the malaria parasite — either *Plasmodium falciparum* or *Plasmodium vivax* — by bites from the female anopheles mosquito. The parasite moves to the liver, then attacks the red blood cells, causing fever, chills and anaemia. Untreated, *Plasmodium faciparum* can block blood cells, causing cerebral malaria and even death, sometimes within 24 hours of the first symptoms.

There were a suspected 2362 cases or malaria reported in Britain among returning travellers last year. Ten people died of the disease. The fatality rate is low: 4 in 1995, 11 in 1994, 4 in 1993 and 9 in 1992. Of the 8355 cases reported here between 1987 and 1992, Dr Ron Behrens of the Hospital for Tropical Diseases in London says half were patients from ethnic minorities visiting family overseas, who wrongly thought they were immune.

Lariam, known generically as mefloquine, emerged in the 1980s as an alternative drug for areas with a growing resistance to chloroquine. They include Kenya, The Gambia, the Amazon basin, Burma, Tanzania, Zambia and the Zambezi valley in

Zimbabwe. Nobody knows exactly how Lariam works, but experts believe it prevents the parasite breaking down a substance in the blood known as haemin, by making the haemin toxic to the parasite.

Research into a new drug stemmed from trying to prevent soldiers from getting ill. In Vietnam in 1965, 800 cases of malaria were recorded a month — as many as the number of evacuated battle casualties. By 1976 Roche won the rights to develop the drug commercially and submitted the results of a series of trials to national licensing bodies, including the US Food and Drug Administration (FDA).

The documents presented to the FDA summarised 10 small-scale trials of the drug on adults and children as a treatment for malaria, plus two similarly small ones into its use in preventing the disease. In all of the trials, some degree of dizziness, palpitations, joint pains and vomiting were reported. But there was little doubt that Lariam worked, and the FDA licensed the drug in 1989. In her report, however, Celia J Maxwell of the FDA said that most of the studies failed to compare mefloquine with other available treatments. “It was therefore difficult to review the data objectively, as no comparison could be made,” she said.

Lariam was licensed for use in the UK in 1990. It became accepted as the main prophylaxis for chloroquine-resistant areas in 1993, after two British travellers — one of them the brother of the Liberal Democrat MP Simon Hughes — died of malaria. Both had taken chloroquine and proguanil (sold as Paludrine).

Reports in the medical press of possible Lariam side effects, including epileptic seizures, depression and psychosis, go back to 1987. Numbness, and a rare but potentially fatal skin reaction known as Stevens-Johnson syndrome, have also been reported.

How did experts reach the conclusion that Lariam was safe enough? Two studies published in 1993 swung the balance by establishing what were considered to be acceptable levels of side effects. The first was a Roche sponsored report by Professor Robert Steffen of the Institute of Social and Preventive Medicine, Zurich University.

It showed that, among 145,000 travellers returning from Africa, the rate of “serious” side effects from taking Lariam — defined as fatal or requiring hospitalisation — was 1 in 10,000. This, said Steffen, compared with 1 in 13,600 for chloroquine. The study concluded that Lariam was 91% effective in chloroquine-resistant areas, compared with 72% effectiveness with a combination of chloroquine and proguanil, a possible alternative.

Also published that year was a study of 1322 Peace Corps volunteers working in west Africa by Dr Hans Lobel, a medical epidemiologist with the US Centers for Disease Control and Prevention. It found “no serious adverse reactions” from Lariam. The findings were disputed by Dr Gordon Cook, a consultant at the Middlesex Hospital in London and an outspoken critic of Lariam. “Every drug has its problems,” he says. “I’m the first to accept that the majority of people on Lariam don’t have any problems. But there is an unacceptable minority that does have side effects of often monstrous proportions, which can often go on for months.”

Lariam was suspected of causing 1505 adverse reactions between February 1990 and April 1998, according to data collected via the Yellow Card scheme, whereby doctors file concerns to the Committee on Safety of Medicines, an advisory body to the Department of Health. Five of these cases were fatalities. The number is small compared with the 18,600 Lariam prescriptions issued in 1996 alone, but surveys show that only 10-15% of suspected adverse reactions are reported. In 1996, 455 were reported, involving 2% of Lariam prescriptions issued. The true incidence of side effects could be much higher.

A survey of 2300 patients by Dr Peter Barrett, chief medical adviser to the Medical Advisory Services for Travellers Abroad (Masta), an information service for the public, found that 1 in 140 travellers on Lariam suffered temporarily disabling side effects severe enough to prevent them from carrying out day-to-day activities. One in 1100 on chloroquine and proguanil suffered similar effects. These figures, published in the British Medical Journal in 1996, contrast with the 1:10,000 cited by Steffen, although

Barrett’s study included cases that did not lead to hospitalisation or death.

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Epilepsy is one of the conditions specifically ruled out for potential users of Lariam. So when Eric Docker, a 50-year-old detective superintendent with the Metropolitan Police, booked a safari in Kenya in October 1996 and was prescribed the drug, he had no reason to worry. Neither he nor his family had a history of epilepsy. “On the warning leaflet it says, don’t take Lariam if you suffer from epilepsy, but I don’t,” he says. He took two tablets before flying out to Kenya, and felt fine until day three of the holiday. He and his wife, Sandra, had spent the night at Treetops, the game-viewing lodge in Mount Kenya national park, and were collecting their luggage from a nearby hotel.

“I was standing outside the hotel, but then I don’t remember anything else,” he says. “It was a dreadful sight — Eric had collapsed,” says Sandra, who had refused Lariam. “He was ashen, glazed-looking and clawing at the air. I thought he was dying.” Docker had two grand-mal epileptic seizures that day, the second one soon after the hotel doctor, Dr Ajay Chhaniyara, arrived. Chhaniyara believes Lariam was the cause and has since told The Sunday Times that he has seen at least a dozen similar cases in the past five years.

The couple returned to Britain a week early. Once home, Docker had three months off work with depression, mood swings, weight loss and nightmares. He lost his driving licence because of the fits. He went back to work in January 1997, but lasted just two months before going off sick again. “I was getting so terribly depressed, unable to make decisions or cope with any of the things I normally cope with. For once in my life, I had no faith in my ability to do my job.”

An initial EEG (electroencephalogram), a test that measures electrical activity in the brain, showed an underlying tendency to epilepsy. Although his consultant ruled out Lariam as the trigger for the attacks, he decided to take Docker off anti-epileptic drugs. Docker has had no further fits and is now working again. A second

consultant has since attributed his two attacks to Lariam.

Docker is not alone: 15 grand-mal seizures have been reported to the Committee on the Safety of Medicines, all of them in people believed to have no history of epilepsy. One of the country’s top epilepsy experts, Professor Martin Brodie of Glasgow’s Western Infirmary, has two other patients — not yet reported under the Yellow Card scheme — who similarly attribute their epileptic fits to taking Lariam. “It’s not uncommon for drugs to reduce seizure thresholds,” Brodie says. “But this certainly suggests to me that Lariam has convulsant properties.”

The epileptic incidences also concern one of the country’s proponents of Lariam, Dr David Warhursr, co-director of the Malaria Reference Laboratory, a research unit based at the London School of Hygiene and Tropical Medicine: “Obviously it indicates that there is something wrong,” he says.

Lorraine Traer-Clark collapsed in January 1995 after taking Lariam for six months while working in Tanzania for an international mining company. She spent two days in bed with severe dizziness, weakness and headaches, then put herself on a flight home. “Don’t ask me how I did it. It was terrible — just awful. But I felt I would rather die on the flight than in Tanzania. I was shaking, sweating hot and giddy. And I was scared.”

Once home, Traer-Clark spent three months in bed, needing constant attention. She had muscle spasms, a slow heartbeat and dizziness, and is still affected three years later. “I can’t do anything,” she says. “I’m basically housebound?” After a year off work sick, she took redundancy. From her home in Romford, Essex, she set up a support group for other people who believe themselves to be victims of Lariam. So far, she has heard from nearly 400, 60% of them women.

The co-founder of Lariam Action, Lance Cole, a 36-year-old transport journalist, first took the drug for a trip up the Zambezi river in 1991, felt ill and was treated for malaria, although tests later were negative. The following year, he took Lariam before visiting Zimbabwe, suffered a racing heart and dizziness, but showed nothing wrong.

In 1994, Cole went to Bali and took Lariam again. "I felt like I had never felt in my entire life before — extreme anxiety and panic." He collapsed, was hospitalised and spent two days in bed. He also had skin rashes on his legs and chest. "I couldn't remember where I was or people's names." He flew to relatives in Australia and then back to Britain, and has spent the past three years living with his mother in Swindon, struggling to resume a normal life.

"Every day has been a challenge. I've lived and worked in Africa, worked in the Vietnamese refugee camps in Hong Kong. I've seen just about everything there is to see. None of it ever fazed me. I never had a problem, only to be completely poleaxed by a little white pill."

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Few of us consider the health risks of a holiday when browsing through brochures. But we should, argues Dr Ron Behrens — and not just the risk of disease, but the risk of adverse reactions to any prophylactic drug we might take. "One can't expect to go to Kenya and have no risk at all," he says. "I think that drug side effects are one of the risks one has to accept:"

Professor David Bradley from the London School of Hygiene and Tropical Medicine, and chair of the Department of Health's Malaria Advisory Committee, is the country's leading authority on the disease. He admits it is hard to balance the chance of being infected by chloroquine-resistant malaria against the risk of drug side effects. "We are really doing sums which have a high degree of uncertainty," he says. On the basis of available data, he estimates that, if 10,000 people went to Africa for a two-week holiday and took no antimalarial drugs, 60 would catch malaria on the east coast and 400 in the higher-risk west. Of those 400, 2 could die. If all took chloroquine and proguanil, between 6 and 120 might contract malaria. On Lariam, only 2 to 40 might contract the disease. But he calculates that 50 people could expect neuro-psychiatric side effects from Lariam — double the rate for chloroquine and proguanil.

Bradley argues that epilepsy and psychosis can also occur with chloroquine. But his own report stated that would only happen to 25 of his 10,000 travellers, compared with 50 on Lariam. "I lie awake about both sides," he says. "I find it extremely difficult to get the right balance. I do feel very concerned about people who get malaria and people who get side effects. I have never said any drug was a safe drug. Nor is going into malarious areas. People should balance things carefully and get the best advice they can — and accept nothing is 100% safe."

Nor are the malaria prophylactics on offer 100% effective. Travellers should also use mosquito repellent and mosquito nets in high-risk areas, and get immediate treatment for any flu-like symptoms.

After more than 18 months deliberation, in September last year Bradley rewrote the malaria guidelines, advising people setting out on a two-week beach holiday to east Africa that they need not take Lariam after all — although they still should for safaris.

Roche, for its part, has updated the information issued with Lariam six times, improving warnings on neuro-psychiatric reactions. It continues to argue that Lariam is the most effective drug for chloroquine-resistant areas. It also states that although neuro-psychiatric side effects may be more frequent with Lariam, overall the incidence of side effects is comparable with those for chloroquine and proguanil.

The legal action against Roche is likely to take years, but the battle against malaria continues. A new drug, Malarone, from Glaxo Wellcome, is being tested as a prophylaxis. A long-established antibiotic, doxycycline, used to treat acne, has also been shown to be effective against chloroquine-resistant malaria, although it is not licensed for this use.

While many agree that there is no simple solution, the role of the Malaria Advisory Committee has been strongly criticised. Major Ashley Croft, a leading medical adviser at the Ministry of Defence, says: "The plan seems to be, let's try to sit this one out and hope the fuss goes away."

Helen Whitehead, meanwhile, is left trying to pick up the pieces of her youth. "I thought it was like an aspirin. I didn't realise how serious a drug it was."

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