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## MALARIA DRUG MAY CAUSE PATIENTS TO BECOME VIOLENT

JENNIFER WESTAWAY (CBC-R): The American army is investigating a string of murders this summer. The victims are all wives of U.S. soldiers. One of the possible common links in their deaths, their husbands were given the anti-malarial drug Larium, also known by its generic name mefloquine.

It's not the first time this drug has been linked to violence in the military. It also cropped up during the Somalia inquiry three years ago. Joining me from Ottawa to discuss the possible side effects of mefloquine is Doctor Michelle Brill-Edwards. She's a drug safety expert who worked with Health Canada at the time of the Somalia enquiry.

Good morning.

DOCTOR MICHELLE BRILL-EDWARDS (Drug safety expert): Good morning.

WESTAWAY: What can you tell me about the history of mefloquine? What's it been used for and for how long in Canada?

BRILL-EDWARDS: Well, this is a drug with a long and troubled history, but it was discovered by the American military, the military Doctors of Walter Reid Hospital and was developed jointly over the past few decades by the U.S. military, Hoffman-Laroche, a pharmaceutical firm, and the World Health Organization.

So since its discovery in the early '70s, there have been a number of countries that have marketed the drug, first in the early '80s in Europe and then later, in the early '90s in North America. And unhappily, the incidence of very severe side effect has been in dispute pretty much throughout the time of development.

WESTAWAY: What is that side effect?

BRILL-EDWARDS: Well firstly, I should mention that there's a spectrum of what you could... as lay people understand this affects on the brain, or neuro-psychiatric side effects. Some of these are very common, every day problems that are not so severe, things like disturbed sleep, terrible dreams and so forth.

But the more severe end of that spectrum of effects on the brain are actual psychosis, what we call acute psychosis, which, in lay terms, would be going crazy, someone who is out of touch with reality and whose actions can be bizarre. In particular, a big concern had been unexplained feelings of suicide and homicide.

And this is where the link to the military comes in. in some instances; we have actual homicide and suicide. And there has been this unanswered question about the influence of mefloquine in tipping the balance and making the military men more likely to behave this way.

WESTAWAY: Well, one of the things that pertains in these cases in the United States is they're all out of Fort Bragg, North Carolina. Three of the soldiers served in Afghanistan and would've had, I suspect, a difficult re-entry anyway. They were coming from things like Special Forces, Delta Force and the Green Berets. How likely does it strike you that this drug might have been involved in their later behaviour?

BRILL-EDWARDS: Firstly, I think it's important to say that no one should jump to conclusions here. There will be an investigation and we must not pre-judge outcome. Certainly, there's good cause to be concerned and to investigate. Just as we must not jump to conclusions, we equally mustn't run away from the possibility that mefloquine had an influence in what happened here.

It's important to understand that if a drug tips the balance toward a particular behaviour, it will be easier to dismiss that and indeed, that seems to be what has happened, in some of the earlier studies.

WESTAWAY: Because the behaviour was already there to some extent?

BRILL-EDWARDS: Exactly. If a drug makes you more anxious and more aggressive then, that influence is likely to become manifest in circumstances like we see with the military, where they're under tremendous stress, where they're trained to be aggressive, where they have been ordered to take the drug rather than carefully be considered as individuals who may not be properly suited to take the drug.

And certainly, there's another influence in the harm setting. Usually, there's a very strict order to not use this drug with alcohol. And the U.S. military has a good track record of trying to keep their military men dry in the field of battle. But once they return home, of course, then that restriction is off and alcohol may become a question. And we know that the drug lasts for a very long time in the body and this mixture may be lethal.

WESTAWAY: I mentioned earlier that this drug, of course, came up during the Somalia enquiry as possibly involved in the Somalia affair. Was a connection ever proven between the drug and the events there?

BRILL-EDWARDS: That's a very good point that you raised, because the Canadian military, even quite recently, are trying to claim that this linkage of mefloquine to suicide and homicidal behaviour in Somalia has been well-investigated by the Somalia enquiry, and that no linkage was found.

And both those statements are categorically false. The Somalia enquiry report clearly states that they regret that they did not have time to address the issue of the linkage to mefloquine to aggressive behaviour, and furthermore states that they wish they had had the time before they were prematurely shut down by the Prime Minister to make that investigation, because they believe that it is a question that is a serious question, that needs to be answered.

WESTAWAY: Why do you think it's still being prescribed to soldiers if there are questions being raised in the United States, to some extent in Canada, and in Britain about the use of the drug?

BRILL-EDWARDS: I think that the drug... We can't lose sight of the fact that this was a drug that was developed by the military. So that it was early on seen as a real feather in their cap. And it's very hard when you've been part of the effort to bring a drug to market to then say: No, we weren't as smart as we thought we were and the incidence of the serious side-effects is not rare, but is actually reasonably common and we now have to take that into account.

So I think military, the company and the regulators have been slow to acknowledge that they got it wrong in the beginning.

WESTAWAY: Is that right, that the side-effects are not rare, because I thought this particular acute psychosis was actually rare in the use of the drug.

BRILL-EDWARDS: Right. Again, we have to be careful about this issue of the spectrum of disease and the minor, or lesser effects on the brain are very common, 10, 20 percent of people.

But the rare - so-called rare - psychiatric side-effects may occur as much as one in a hundred, whereas before we thought in the order of one in the order of one in 12 000.

Now you might say: Well, how did that come about, that we made that impression? There was a study done that gave rise to this one in 12 000. But even as a layperson, you can see that the study was not designed to give an accurate answer on this score; Questionnaires were handed out to people returning from African who would have taken mefloquine as prophylaxis.

And you could see that someone that has committed suicide is not going to be on the plane coming home. Equally, someone who has committed homicide, somebody who has attempted these things is not likely to admit it on the questionnaire, especially if the questionnaire doesn't ask that particular question.

So when we go back and say: Where did this figure come from, we realize that really, the so-called scientific studies that suggest one in 12 000 are very sadly lacking.

There is one study done by the military that was a carefully-done study that watched military men taking the drug in the field and they were seen weekly.

And it's a very interesting point that in that study, two men had to be withdrawn from the study because of suicidal ideation.

WESTAWAY: What military was this?

BRILL-EDWARDS: This was the American military. And interestingly, of the 203 - I think it was - men in the study who had mefloquine doses use in prophylaxis, two developed suicidal ideation. That would suggest that we're dealing with a serious psychiatric side-effect rate that is in the order of one in 100, not one in 12 000.

WESTAWAY: More serious than we had previously thought.

BRILL-EDWARDS: Much more so. And also it then starts to... You start to say: Well, what is the risk of getting malaria? And is that one in 100 risk of becoming suicidal or homicidal worth it?

WESTAWAY: Worth it...

BRILL-EDWARDS: It changes the whole balance of whether and when this drug should be used in comparison with other drugs.

WESTAWAY: Thank you for joining us this morning/

BRILL-EDWARDS: You're welcome.

WESTAWAY: Doctor Michelle Brill-Edwards is a drug-safety expert in private practice in Canada.

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