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'Unprecedented' brain reaction caused French drug trial death: experts

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Experts investigating the death of a man in a drug trial in France said Monday that the compound being tested had caused an "astonishing and unprecedented" reaction in the brain.

Six people were hospitalised and one died in January after taking part in a Phase I trial for a new pain and mood disorder medication at the Biotrial research institute, in western France, on behalf of Portuguese pharmaceutical company Bial.

In a report published on Monday, a group of experts put together by the National Agency for Drug Safety said the problem clearly lay with the substance being tested—BIA 10-2474.

They underlined "the astonishing and unprecedented nature" of the accident, which caused a reaction in the brain "unlike anything seen before".

The team ruled out any manufacturing problem, and said there was no shared genetic weakness among the victims, who suffered similar damage to the same part of the brain.

However it was noted that the drug test volunteers were relatively old (aged up to 49) and some presented various risk factors "vis a vis certain adverse drug reactions".

Pharma company Bial told AFP that "the results obtained in these pre-

clinical didn't raise any issue regarding the toxicity/dangerousness of the molecule."

BIA 10-2474 is part of a family of FAAH-enzyme inhibitors that can have an impact on pain and anxiety by boosting the endocannabinoid system involved in appetite control, pain sensation, mood and memory.

"It is clearly the molecule that is the cause. The common element between the victims is indeed that molecule," said Dominique Martin, director general of the drug safety agency, following the publication of the report.

High doses

The experts wrote that "BIA 10-2474 was administered to the volunteers at a dose 10 times greater than that needed to completely inhibit the FAAH enzyme".

But they added that "the stimulation, even massive, of the endocannabinoid system... is not known to cause very serious toxic effects in itself."

A total of 108 volunteers took part in the study. Ninety received the drug at varying doses, and the rest were given a placebo. Those hospitalised had received the highest dose.

One question the experts want answered is why so much animal testing had preceded the human trials.

They said it was surprising to see that rats, mice, dogs and monkeys were all used—raising the question whether the lab had suspicions about toxicity.

The pain relief effects observed in the animals, added the team, appeared "much too superficial" to warrant human testing.

No ill-effects were noted in the animals, despite doses 400 times stronger than those given to the human volunteers.

But other laboratories had already abandoned efforts to develop this family of molecules "due to ineffectiveness", the experts said.

The hospitalised volunteers received cumulative doses of between 250 and 300 milligrammes. The report criticised the large daily dose of 50 mg they were given—a major leap from the previous maximum of 20 mg per day.

It was not clear why three of the six victims had a more serious reaction, including the one death, while two experienced less severe problems and one none at all.

There was no evidence of drug or alcohol use among the group.

The experts will formally present their conclusions on March 24.