Experts: Patches + heat = danger; Heat can make medicated patches unsafe, even deadly, experts say. The FDA is taking a look.

The Philadelphia Inquirer

March 5, 2006 Sunday

The Philadelphia Inquirer
Found on Philly.com

Section: NATIONAL; Pg. A01

Length: 2200 words

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Body

Medical experts say medicated patches, used by 12 million people for a range of ailments, can become unsafe when heated by exercise, soaking in a hot tub, or even a high fever. And they think patients should be warned.

"Most people don't realize that heat is going to increase absorption rates, even to toxic levels," said Michael Cohen, director of the Institute for Safe Medication Practices, an industry watchdog in Huntingdon Valley.

Last week, the Food and Drug Administration said it was launching an "exhaustive review" of the safety of the patches themselves. Part of the review specifically studies how heat affects the products.

The FDA investigation comes eight months after the agency announced a probe into 120 deaths linked to fentanyl patches, which are used for chronic pain. In November, the agency issued a warning about birth-control patches after a study showed that women who wore the patch had 60 percent more estrogen in their blood than those on the pill.

In the last 25 years, patch medications have morphed from a simple motion-sickness drug to more than 30 prescription patches used by 12 million people worldwide for ailments ranging from bladder control to heart disease. Companies are marketing more and more versions - the first antidepressant patch was approved Monday.

Experts say that heat increases the absorption rate on all of them.

That's because all patches work the same way: The drug seeps through the skin into the bloodstream, and increased blood flow causes the body to absorb the drug faster, said Bozena B. Michniak, who studies ***transdermal*** patch delivery at the Center for Biomaterials at Rutgers University's Piscataway campus.

But not all hot patches will necessarily cause harm.

"It depends on the drug and the patch," Michniak said. "We could all say there will be an effect and absorption rate will increase, but how much? Many factors play a role."

The problem is most evident with the fentanyl patch, which is 100 times more potent than morphine. Since it was introduced in 1990, the drug has been linked to 120 deaths, the FDA reported.

FDA officials say that as few as 1 percent of all serious side effects are reported to the agency. Its database does not give details about the cause of death. The agency has been criticized, most recently in the recall on the arthritis pill Vioxx, for not paying attention to problems early on.

Whether a drug comes in a patch or not, the FDA does not say how many deaths should trigger an investigation or a recall. In 2000, the agency pulled the diabetes drug Rezulin after it was tied to 63 liver-failure deaths. Lotronex, a drug for irritable bowel syndrome, was recalled after it was linked to five deaths.

In 2004, patches overall were cited as the primary cause of death in eight cases, including two teens on birth-control patches, according to an Inquirer analysis of an FDA database.

In 2003, three people died, including a 45-year-old man and a 58-year-old woman on fentanyl pain patches.

Both years, the patch was a primary suspect in at least 30 cases in which patients were hospitalized, disabled or left with a life-threatening complication.

"The problems are real, they're happening and they're underreported," said Cohen, who sits on the FDA's Drug Safety and Risk Management Advisory Committee. "It's possible for people to get hurt."

The FDA database, the Adverse Event Reporting System, is based on mandatory reports of all kinds of drug reactions from pharmaceutical companies and voluntary data from doctors and hospitals. The data do not include whether heat was a factor in the problem, but mention the name of the drug, and whether it was a primary, secondary or concomitant factor in the incident.

The FDA database does not indicate with certainty that the suspected drug caused a reaction and does not include final investigation results.

Studies as early as 1986 showed that heat can double the rate at which the body absorbs medication, but there were no public warnings until 1994.

That came after the death of a 36-year-old Montgomery County man.

Kurt Hophan was given a fentanyl pain patch after a back injury. He went to his bedroom at his mother's house in Glenside and fell asleep with a heating pad and an electric blanket.

"When the heat from the pad and the electric blanket came into contact with the patch, the amount of fentanyl released into Mr. Hophan's bloodstream was approximately one hundred (100) times greater than the amount prescribed," according to the judge's ruling in a lawsuit filed against the drug's manufacturer by his mother, Elaine Hophan.

He never woke up. He died on March 4, 1994.

In 2001, a jury awarded his mother $5 million in compensatory damages. After an appeal, the case was settled under a confidential agreement, said Stephen Raynes, who represented Elaine Hophan.

The warning appeared three months after Hophan's death. Johnson & Johnson declined further comment.

There's no question that there are benefits to patch medication, and that millions of consumers use patches safely.

They are easier on the body because medicine is absorbed through the skin into the bloodstream, without a "first pass" through the liver and the stomach. That often means a smaller dose is required.

Plus, it's convenient.

"Patches improve compliance, particularly for people who have to take medication several times a day or for people who forget," said Sean Hennessy, pharmacology professor at the University of Pennsylvania and another member of the FDA's drug safety committee.

And they are popular. In 2004, patch sales totaled about $3.4 billion, according to Greystone Associates, a medical market-research firm in New Hampshire.

The patch comes in two main forms: the liquid reservoir and the matrix.

In the liquid-reservoir version, such as the fentanyl patch, the medicine is embedded into a gel-like substance in the center, and released through a membrane into the skin.

The matrix patches contain the medication within the adhesive that adheres to the skin, often using the flesh as the rate control - because the skin can absorb only so much, so fast.

The patch is not for every drug, said John Urquhart, professor of biopharmaceutical sciences at the University of California at San Francisco and one of the creators of the original motion-sickness patch.

"A lot of morons out there think you can put a drug in a patch and it will sell like hotcakes," Urquhart said.

To work well in a patch-delivery system, he said, the drug has to be effective in small doses. The medicine should not cause irritation (which increases absorption), and should have a wide safety margin to prevent accidental overdose, which can occur when it is heated.

Multiple studies have shown that heat has a sharp effect. A 1986 study found that just 20 minutes of bicycling with a nitroglycerin heart medication patch increased concentration of the drug twofold to threefold. Similar results were found after 30 minutes in a sauna.

"In chemistry, if we want to speed up a reaction, you apply heat," said Robert Middleberg, laboratory director of National Medical Services in Willow Grove. "It's silly for us to believe that heat wouldn't play a factor in a drug-delivery device that works with the skin."

The independent lab receives thousands of unexplained-death cases from medical examiner's offices nationwide. Of the 100 or so patch-related deaths he gets each year, about 70 percent are caused by patient misuse and 15 percent more are due to drug abuse. The rest, Middleberg said, cannot be explained, and he thinks they are likely due to a problem with the patch.

"The dynamics of the patches are not really completely understood," he said.

Most of the patch-related deaths that Middleberg sees involve fentanyl.

"You find reports of death with other patches, most notably nitroglycerin patches," he said. "But they are really hard to prove because nitro just falls apart in the body and you're left wondering what really happened."

One company, ZARS Pharma, based in Salt Lake City, specifically uses heat with its patch products, including an anesthetic one approved by the FDA in June and marketed by a Chadds Ford company, Endo Pharmaceuticals Holdings Inc.

Their two patch products work differently. The pain patch, under development, comes with a separate device, similar to a heating pad, that is placed over it. The anesthetic patch heats up when exposed to air, much like over-the-counter hand warmers.

Skin temperature is usually about 89.6 degrees Fahrenheit, but increasing that temperature up to about 102 degrees can quadruple the absorption rate, said Michael Ashburn, ZARS vice president for clinical and regulatory affairs. That can happen in as little as 20 minutes, he said.

"You have to be able to control the temperature so we know what's getting through," Ashburn said.

Although uncontrolled amounts of narcotics, such as fentanyl, could have fatal results, it's unclear what higher doses of other drugs could do.

"I don't think you can kill yourself with a nitro patch; you'll just make yourself feel dizzy," said Gordon Flynn, professor of pharmaceutics at the University of Michigan and a consultant for Mylan Pharmaceuticals Inc. "You're not supposed to be on it continuously."

In December, the FDA began to study how heat affects the absorption rates of all patches under various circumstances, said Lucinda Buhse, director of the FDA's Division of Pharmaceutical Analysis.

"We would like to develop a method that's applicable across the board with different drugs and different patches," she said.

The investigation will focus on fentanyl and birth-control patches first, to see how they react to hot tub and sauna heat, among other scenarios.

Douglas Stokke, a spokesman for Johnson & Johnson, which makes the fentanyl patch and Ortho Evra birth-control patch, said the company did not have clear information about the FDA study. When asked whether doctors should warn patients about exposure to heat while wearing a patch, he said: "Physicians should be knowledgeable about the prescribing information for these products and should be prescribing them according to labeling."

But, says Michniak, of Rutgers, those who use patches should be careful about sitting in the sun, using heating pads, or doing anything else that might increase the skin temperature for a long time.

"If it's not in the patient insert, they may not be as aware as they should be," she said.

One patch whose safety is being questioned is the Ortho Evra birth-control patch. Last year, doctors wrote more than 9.4 million prescriptions for it, according to IMS Health, an industry monitoring firm based in Plymouth Meeting.

In November, the FDA released a study saying that women who wore the patch had far more estrogen in their bloodstream than those who took the pill. Researchers aren't sure why. Four months later, Johnson & Johnson released a study stating that women who wore the patch had twice the number of blood clots, which can cause strokes and heart attacks.

On the same day, another study, published in the journal Contraception, said there was no additional risk compared with the pill's risks.

Vanessa Cullins, an ob/gyn and vice president for medical affairs for Planned Parenthood, said the patch came under fire unfairly.

In the J&J study, Cullins noted that rates for blood clots were as high as four per 10,000 on the pill and eight per 10,000 on the patch.

Cullins said that, even if the increase was real, "it's still a very rare event."

Women should weigh the risks and benefits of the patch, she said, noting that it may not be appropriate for those with a family history of blood clots or strokes.

Since July, more than 40 lawsuits have been filed nationwide, claiming that blood clots caused by the patch killed or injured women.

While studies into patch safety continue, more proposals for new ***transdermal*** medications are appearing before the FDA.

Next up is Daytrana, a controversial methylphenidate patch specifically for children with attention deficit hyperactivity disorder. In June, FDA medical officer Robert Levin said the patch resulted in "excessive drug exposure at inappropriate times," vomiting, and a high risk of causing a tic. He suggested that it not be approved.

Seven months later, Levin changed his mind. In December, he told an FDA advisory committee that the patch, aimed at 6- to 12-year-old children, did not cause significantly different problems than Concerta, an ADHD pill. With one exception: Up to 22 percent of those who used the patch became so sensitive to it that they could never take the drug methylphenidate again, in any form.

The ADHD patch lasts nine hours, and members worried that children would be responsible for their removal and not take it off in time. "Theoretically, it is possible that continued exposure could increase the risk of insomnia and other adverse events," Levin said.

The FDA did not respond to multiple requests to interview Levin and to questions about the database.

The committee unanimously recommended the patch, but only for children who cannot swallow pills. It is now under FDA review.

Post a question for ***Dawn Fallik*** at *http://go.philly.com/askdawn*. She can be contacted directly at *dfallik@phillynews.com* or 215-854-2795.

Classification

Language: ENGLISH

Publication-Type: Newspaper

Subject: DISEASES & DISORDERS (90%); INVESTIGATIONS (90%); SAFETY (90%); DEATH & DYING (89%); NARCOTICS (89%); PAIN MANAGEMENT (88%); DRUG SAFETY (78%); FEDERAL INVESTIGATIONS (78%); CHRONIC DISEASES (77%); ARTHRITIS (76%); DRUG & MEDICAL DEVICES APPROVAL (76%); GASTROINTESTINAL DISORDERS (73%); HEART DISEASE (73%); APPROVALS (72%); DIABETES (72%); PHARMACEUTICALS ASSOCIATIONS (71%); IRRITABLE BOWEL SYNDROME (68%); COLON DISEASE (66%); BIOMATERIALS (64%)

Organization: FOOD & DRUG ADMINISTRATION (93%)

Industry: ***TRANSDERMAL*** DRUG DELIVERY (90%); NARCOTICS (89%); ANALGESICS (88%); BIOMEDICAL & DENTAL MATERIALS (79%); ANTIDEPRESSANTS (78%); DRUG DELIVERY SYSTEMS (78%); DRUG SAFETY (78%); CENTRAL NERVOUS SYSTEM DRUGS (77%); DRUG & MEDICAL DEVICES APPROVAL (76%); GASTROINTESTINAL AGENTS (76%); NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (76%); PRESCRIPTION DRUGS (76%); ANESTHETICS (74%); PSYCHOTROPIC DRUGS (73%); PHARMACEUTICALS ASSOCIATIONS (71%); BIOMATERIALS (64%)

Geographic: PHILADELPHIA, PA, USA (78%)

Load-Date: March 5, 2006

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