

Anti-inflammatory drug effective for treating lymphedema symptoms

October 18 2018



Human skin structure. Credit: Wikipedia

For more than three decades, Lisa Hanson did her best to hide the unsightly fluid retention in her left leg that caused uncomfortable swelling and made her skin taut and thickened. At 17, when she was first diagnosed with lymphedema, she threw out her shorts and dresses and began a lifelong journey of wearing compression hose up to her thigh

and using an electric sleevelike pump every night to control the swelling.

Now, with a new treatment in hand, she's actually excited to tell people about this chronic condition, which before, she said, left her feeling like "a freak."

"For a long time I couldn't talk to people about my [lymphedema](#) without crying because it's something weird and obscure," Hanson said. "Now there is hope for people like me with this disease."

Hanson took part in one of two small clinical trials led by researchers at the Stanford University School of Medicine which showed that ketoprofen, an inflammation-reducing drug available by prescription and currently approved by the Food and Drug Administration, can effectively treat symptoms of lymphedema and help ease the daily burden of care.

"Ketoprofen restores the health and elasticity of the skin," said Stanley Rockson, MD, professor of cardiovascular medicine at Stanford. "I believe it will reduce recurrent infection. It can also reduce swelling."

A paper describing the findings of the two [clinical trials](#) will be published Oct. 18 in *JCI Insight*. Rockson is the lead author. Mark Nicolls, MD, professor of pulmonary and critical care medicine at Stanford, is his principal collaborator. They both served as corresponding authors for the manuscript.

"So many patients have gone through decades being told there is no medical treatment," said Rockson, who holds the Allan and Tina Neill Professorship of Lymphatic Research and Medicine. "Now, they can go to a drugstore and get a pill with a doctor's prescription. This new treatment doesn't cure lymphedema, but our studies show it has the capacity to make the illness more livable, more workable."

Painful swelling

Lymphedema is a common but often ignored condition that stems from a damaged lymphatic system and results in swelling in one or more parts of the body, usually the legs. It can be hereditary or it can occur after a surgical procedure, infection, radiation or other physical trauma. The swelling, caused by a buildup of lymph fluid within the various layers of the skin, increases the risk of infections and can cause debilitating pain and a thickening of the skin that can restrict movement. There is no cure, and there has been no drug therapy available.

Ever since Hanson was diagnosed in her teens, the only available treatment has been to wear compression garments; use the electric pump, which moves the excess fluid from her leg back into the bloodstream; or get massage therapy to suppress the swelling, which can occur throughout the body. She has done all of this religiously for decades.

"It's been a lot of work and a lot of burden putting the compression socks on daily," Hanson said. "It's hard to get them on and off. They're tight and they're heavy. I've used the pump every night sometimes for up to four hours."

As many as 10 million Americans and hundreds of millions of people worldwide suffer from the condition, many from the aftereffects of cancer treatments. Thirty percent of women treated for breast cancer get lymphedema, usually as a result of radiation treatment and lymph node removal, according to the American Cancer Society.

Years ago, Rockson, a physician-scientist who has treated thousands of patients with lymphedema, began to suspect that inflammation was a root cause of the disease. To test his theory, he created a mouse model for lymphedema—the disease would manifest in the animals' tails—and treated it with ketoprofen, a nonsteroidal anti-inflammatory drug, or

NSAID.

"It reversed the lymphedema," Rockson said. "We saw tremendous improvement in the structural abnormalities in the skin."

To test ketoprofen in humans, Rockson conducted two pilot trials, which are both discussed in the paper. The first trial had 21 participants who knew they were getting the drug and took it orally for four months. Researchers performed skin biopsies at the beginning of the trial and then four months later at the end of the trial as a measurement of disease severity.

"That was an extremely positive trial," Rockson said. "We saw a tremendous reversal in the disease process in the skin and dramatic reductions in skin thickness." This led to the second double-blind, placebo-controlled study with 34 participants. Hanson, who participated in the second trial, didn't know at first whether she was taking ketoprofen or a placebo. But she felt fairly certain after two months that she was getting ketoprofen.

"After a couple of months, I remember going home one day and taking my compression stockings off and looking at my leg thinking, 'Wow my skin is wrinkly, that's so weird.' The skin wasn't so taut or thick. It was more like normal," Hanson said.

Thinner skin

The second trial further validated that the drug can reduce thickening of the skin. Researchers also examined the anatomy of the skin cells and confirmed that ketoprofen worked by unblocking the molecular pathway that was causing the inflammation and restricting the body's ability to repair its own lymphatic system.

"When you look at skin from lymphedema patients under the microscope, you see a dramatic increase in cell density and increase in connective tissues and fluid around the cells," he said. "What we saw in skin biopsies after the four months of ketoprofen was a reduction in that thickness. All that cell density went away."

Results showed that ketoprofen made the skin healthier and more elastic, Rockson said.

"Anecdotally, we also got the impression that the patients who were treated saw a dramatic decrease in infections, although this analysis wasn't part of the study," Rockson said.

After the four months, the patients in the second trial were "unblinded" and given the option to continue using the drug by prescription, Rockson said. All chose to continue taking the drug, including Hanson, who has now taken the ketoprofen for several years.

"Over time, the swelling has gone down," she said. "It's not a cure. It doesn't make it go away, but it has been easier to take care of my leg." She still wears the compression stockings, but they're much easier to tug on, and the nightly pumping now takes just a fraction of the time it used to.

Hanson, like other participants in the trial, was warned by researchers that past studies have shown gastrointestinal and cardiovascular side effects from long-term use of ketoprofen in some patients, but she still decided to keep taking the drug.

"For me, the choice of being comfortable and not having so much burden in terms of care is a much greater benefit and outweighs the risk," she said.

An inflammatory response

Just how ketoprofen was working at a molecular level, though, remained unclear early on. To further examine this while continuing his ketoprofen trials in humans, Rockson joined forces with Nicolls, whose lab had been studying the molecular pathways of inflammation in pulmonary hypertension.

"We were excited to finally figure out that the [drug](#) worked by blocking an inflammatory molecule called leukotriene B4," said Nicolls referring to a study published in May 2017.

The researchers found that the buildup of lymph fluid is actually an inflammatory response within the tissue of the [skin](#), not merely a "plumbing" problem within the lymphatic system, as previously thought. They discovered that the naturally occurring inflammatory molecule LTB4 is elevated in both animal models of lymphedema and in humans with the disease, and that at elevated levels it causes tissue inflammation and impaired lymphatic function.

Further research in mice showed that using [ketoprofen](#) to target LTB4 induced lymphatic repair and reversed the disease processes. This indicated that perhaps other therapies could reverse the negative impact of inflammation on lymphatic repair by targeting LTB4.

More information: Stanley G. Rockson et al. Pilot studies demonstrate the potential benefits of antiinflammatory therapy in human lymphedema, *JCI Insight* (2018). [DOI: 10.1172/jci.insight.123775](https://doi.org/10.1172/jci.insight.123775)

Provided by Stanford University Medical Center

Citation: Anti-inflammatory drug effective for treating lymphedema symptoms (2018, October 18) retrieved 26 April 2024 from <https://medicalxpress.com/news/2018-10-anti-inflammatory-drug-effective-lymphedema-symptoms.html>

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