

First do no harm? UH prof taking opposite approach to treat asthma

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Richard Bond, associate professor of pharmacology at UH, pictured in his lab with tools he's used in research that takes a new approach to treating asthma by using a concept called "paradoxical pharmacology." Credit: Thomas Shea

One month of tough breathing may help asthma sufferers breathe easier in the long run, according to research from one University of Houston professor.

In a move that challenges one of the most basic tenets of the Hippocratic Oath – first do no harm – Richard Bond, associate professor of pharmacology at UH, is relying on a long-standing medical taboo to treat asthma. Although counterintuitive, Bond's studies are reminiscent of hair-of-the-dog folk wisdom to treat like with like, in this case using beta blockers (or antagonists) instead of stimulants (or agonists) in

asthmatics.

Coining the term “paradoxical pharmacology” – treating patients with medicine that initially worsens their symptoms before eventually improving their overall health – Bond first applied this hypothesis in studies with mice and then moved on to two clinical trials with humans. Currently in the second clinical trial, the part of this research analyzing mice was recently published in the *American Journal of Respiratory Cell and Molecular Biology*, which cited the relevance of Bond’s work as possibly leading to a paradigm shift in the treatment of asthma. The results of the first human trial were also recently published in *Pulmonary Pharmacology and Therapeutics*.

Acute asthma attacks have traditionally been treated with inhaler-type stimulant drugs that open constricted airways. Giving beta blockers to asthmatics has long been thought to be contraindicated, because their acute use may cause increased airway resistance. While the use of beta-stimulants is known to provide temporary relief, their effectiveness declines over time.

Bond’s tests initially done on asthmatic mice and later replicated in his first clinical trial with humans showed that while beta blockers initially made breathing problems worse, their continued use resulted in improved respiratory function after a 28-day period. These longer-term effects demonstrate that chronic use of beta blockers alleviates asthma by helping the smooth muscle lining the airways to relax and dilate, thereby allowing air to flow more freely.

“In order to move certain ideas forward, science often needs to be a collaborative effort,” Bond said. “You must find the right people willing to act as a team. I have been very lucky in that people have given my ideas a chance.”

Enlisting the help of some pulmonologists in the Texas Medical Center, Bond collaborated with Dr. Nick Hanania at The Baylor College of Medicine on both human trials. Also, Dr. Burton Dickey, chair of the department of pulmonary medicine at M.D. Anderson Cancer Center, and his colleagues decided to assist Bond's research efforts when the mouse studies showed that chronic beta-blocker treatment has significant anti-inflammatory effects.

Using beta blockers when it seems a stimulant is called for defies medical dogma, but this is not a new concept. Bond's work builds on an earlier breakthrough in treating congestive heart failure (CHF), in which case patients had been treated for decades with stimulant drugs to increase cardiac output. Beta blockers were prohibited because they initially further reduced the heart's pumping power, but the stimulants ultimately caused the heart to wear out over time from the increased activity.

About a decade ago, the thinking on beta-blocker therapy was reversed when researchers discovered that although treatment with beta blockers reduced cardiac activity at first, the prognosis reversed itself after two to three months. This treatment shift reduced the mortality rate among CHF patients by up to 65 percent.

"Decades of conventional wisdom were overturned, and beta blockers replaced stimulants as the top drug for CHF patients," Bond said. "For 30 years, intellect told us that beta blockers wouldn't work to treat these patients, and unfortunately millions of heart patients died prematurely. It would be a tragedy to not have learned from that lesson."

With his work based on this precedent, Bond points out that beta blockers are not the only example of paradoxical pharmacology. Hyperactive children are treated with the amphetamine-like Ritalin®, and the skin irritant retinoic acid is used to treat acne. Additionally, there

has been research into using antipsychotic drugs traditionally used for schizophrenic patients to decrease the incidence of Alzheimer's disease by suppressing the dopamine system, which is hypoactive in such neurodegenerative diseases. These examples further the case for investigating paradoxical approaches like Bond's.

In Bond's first clinical trial, he and his colleagues saw similar results in humans to what was seen in the mouse models. Mild asthmatics were treated for nine weeks with the beta blocker nadolol, with all subjects tolerating the drug and 80 percent experiencing a reduction in airway hyperresponsiveness. Laying the groundwork for continuing studies with beta blockers in the treatment of asthma, the results suggest there may be a way to counteract some of the negative aspects of traditional treatments.

"The principle that certain pharmacological compounds have different effects depending upon whether they are given for long or short periods has been demonstrated," Bond said. "And even if I am correct about beta blockers ultimately being used in the treatment of asthma, there probably always will be a need for the inhaler-type agonist drugs to handle acute asthma attacks. I do believe, though, that beta blockers hold promise in a maintenance or preventative regimen that could reduce the number or severity of attacks and improve a patient's quality of life."

This research has received funding from the National Institutes of Health, as well as from two San Francisco-based organizations – a private biotechnology company called Inverseon and the philanthropic Sandler Program for Asthma Research. As the scientific founder of Inverseon, Bond leads a distinguished panel of scientists on the company's advisory board, including Nobel Laureate in Medicine Sir James Black, who is considered the "father of beta blockers."

"If we continue down this path, replicating these results, this paradoxical

approach to asthma treatment may well become an important new approach to asthma therapy,” said Dr. William J. Garner, CEO of Inverseon. “We’ve already engaged in discussions with major pharmaceutical companies about taking this to the next level and are actively seeking additional funding for eventual product development.”

Source: University of Houston

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