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Inhalable form of Ambrisentan drug could offer faster-acting treatment option for pulmonary edema

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In a new study, researchers show an aerosolized, inhalable form of the drug Ambrisentan could offer a faster-acting treatment option for pulmonary edema, a life-threatening condition in which fluid accumulates in the lungs. Pulmonary edema is a significant risk for anyone spending time at high altitudes, and also affects people with chronic conditions including congestive heart failure and sickle cell anemia.

High altitude pulmonary edema, or HAPE, results when exposure to reduced oxygen levels causes the arteries in the lungs to constrict, which in turn causes blood pressure within the lungs to rise. Unchecked, this process leads to the rapid accumulation of fluid in the lungs, further reducing a person's ability to get oxygen and causing severe physical impairment.

Currently, Ambrisentan is available only in pill form and takes time to provide relief. The new study, conducted in rats, showed that delivering the drug via an inhaler achieved the same effect with just one-fifth of the typical oral dose.

"This mode of delivery gets the drug directly to the site of the problem—the lungs—providing relief much faster than the oral treatment," said Scott Ferguson, Ph.D. a postdoctoral researcher at the University of Colorado, Denver Anschutz Medical Center, who conducted the research. "Additionally, it requires a much lower dose, likely lowering the incidence of side effects and the cost of treatment."

Ferguson will present this research at the American Physiological Society Annual Meeting during *Experimental Biology* 2016.

Although it can strike anyone living at or visiting altitudes above 5,000 feet, HAPE is a particularly significant concern among mountain climbers, military personnel and people who ascend to high elevations rapidly. Specific risk factors have not been identified, but genes are thought to play a role in an individual's susceptibility.

"As a climber, I've had very brief experiences with HAPE myself," said Ferguson. "With the fluid buildup in the lungs, you have a lot of coughing going on, shortness of breath, a lot of difficulty breathing. In more severe HAPE, the inability to move oxygen from the atmosphere into the blood can be a real problem, because the best treatment for the affected person is to get them off the mountain, but that's not always possible when they can't move on their own."

Ambrisentan and other drugs reverse the course of HAPE by dilating the pulmonary arteries, allowing oxygen-rich blood to flow more freely. These drugs are typically used when it is not possible to quickly move a patient to lower altitude or if symptoms do not resolve at lower altitude. They can also be used prophylactically to prevent HAPE before a person ascends to high altitude. An inhaler-delivered version of the drug could potentially allow for a quicker, easier response in all of these scenarios.

"I think it's much more practical, especially in military situations," said Ferguson. For example, he said a soldier parachuting into a high-altitude location could take a dose from an inhaler just before leaving the aircraft, reducing the likelihood of developing HAPE on the ground. Or, an inhaler could be carried along in a unit's first-aid kit, allowing a person to get help when symptoms first emerge.

In addition, delivery of the drug directly into the lungs is likely to be associated with fewer side effects than an oral dose, which sends the drug throughout the body.

Pulmonary edema is also a complication of pulmonary hypertension, a chronic increase in blood pressure in the lungs sometimes associated with other diseases, such as heart failure and sickle cell anemia. People with these conditions are at risk of pulmonary edema at any elevation, but the risk increases at higher altitudes, sometimes leading to restrictions on where patients can live or visit. Being able to carry an Ambrisentan inhaler could give such patients more freedom to travel to high-altitude locations.

Ferguson said the approach will need to be tested in people before an Ambrisentan inhaler could be made available in the market. In addition, the team is working to further refine the aerosolized delivery of the drug by developing

microbubbles that surround the droplets and help the drug reach the lowest portion of the lungs, where it has the greatest impact.

This microbubble approach, if successful, could potentially be applied to any inhaler-delivered drug. "If you could use this technology to make inhalers work better and perhaps with even lower doses it's a win-win," said Ferguson.

Source:
Federation of American Societies for Experimental Biology (FASEB)
