Nanoparticle-based battlefield pain treatment moves a step closer

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University of Michigan scientists have developed a combination drug that promises a safer, more precise way for medics and fellow soldiers in battle situations to give a fallen soldier both morphine and a drug that limits morphine's dangerous side effects.

They use nanotechnology to devise ultra-small polymer particles capable of carrying the drugs into the body. The development of the combination drug makes possible a precise feedback system that can safely regulate release of the drugs aboard the nanoparticles.

The scientists at the Michigan Nanotechnology Institute for Medicine and Biological Sciences report their results in the September issue of *Bioorganic & Medicinal Chemistry Letters*.

Soldiers injured in combat typically receive morphine as soon as possible to relieve pain. Morphine, however, also depresses normal breathing and blood pressure, sometimes to life-threatening levels. So medics need to give a short-acting drug that aids normal respiration and heart beat, but in doses that still allow the morphine to relieve pain effectively. Today, achieving that balance is a challenge outside a hospital.

The combination drug that U-M scientists have developed promises to make balanced treatment possible even in combat zones, says James R. Baker, Jr., M.D., director of the Michigan Nanotechnology Institute for Medicine and Biological Sciences (MNIMBS) and the study's senior

author.

"This system could improve pain management for millions of patients with chronic illnesses," says Baker, Ruth Dow Doan Professor and allergy division chief in the U-M Department of Internal Medicine.

The long-range goal of the research, funded by the U.S. Defense Advanced Research Projects Agency, is to develop a practical method that medics or soldiers themselves could administer, perhaps using an auto-injector device.

U-M chemists screened several compounds to search for a successful "pro drug," a drug that can release or become another drug. In this case, they wanted one that could convert to Naloxone, a drug now used to counter morphine's effects, but would activate only when blood oxygen levels drop too low. In laboratory tests using human plasma, one pro drug successfully sensed oxygen levels and turned on or off as needed.

"When respiratory distress is too severe, that will trigger release of Naloxone, the antagonist (morphine-suppressing) drug. When the oxygen blood levels go up, that will stop the action of the antagonist drug and more morphine will be available," says Baohua Huang, Ph.D., the study's first author and a research investigator at the Michigan Nanotechnology Institute and in Internal Medicine.

MNIMBS scientists are proceeding with animal studies of the pro drug's effects and will develop a dendrimer that can carry the pro drug and morphine, using a dendrimer platform technology previously developed at U-M. They hope to advance to more animal and eventually human studies.

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