Reformulated imatinib eliminates morphine tolerance in lab studies

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By reformulating the common cancer drug imatinib (Gleevec), researchers have eliminated morphine tolerance in rats – an important step toward improving the effectiveness of chronic pain management in patients, according to researchers at The University of Texas MD Anderson Cancer Center.

Narcotics such as morphine are a mainstay of chronic pain treatment. Over time, tolerance to the pain-relieving effects of these drugs can develop, requiring increasing doses to control pain. In some cases, narcotics become ineffective. This study, published online in *Nature Medicine*, is the first to identify a cellular signal that selectively causes narcotic tolerance.

"By suggesting a way to prevent or reverse tolerance in patients, this study could have far-reaching implications for many people suffering with chronic intractable pain," said senior author Howard B. Gutstein, M.D., professor in the Departments of Anesthesiology/Perioperative Medicine and Biochemistry at MD Anderson.

One imatinib target causes morphine tolerance

In the study, scientists discovered that activating the β - isoform of the platelet-derived growth factor receptor (PDGFR) caused morphine tolerance in animals not previously exposed to morphine.

Imatinib is commonly used to treat certain types of leukemia and gastrointestinal tumors. It targets a number of cellular receptors, including the PDGFR, which is heavily expressed in those cancer cells.

In this study, imatinib prevented morphine tolerance, and importantly, completely reversed tolerance in rats that received high morphine doses continuously for several days, which reflects how morphine and other opioids are often given to chronic pain patients.

Researchers modify imatinib to block PDGFR

Morphine and other opioids work by binding to mu opioid receptorsin the brain and spinal cord.

Imatinib's ability to inhibit morphine tolerance has not yet been observed in cancer patients who take imatinib because the drug does not penetrate the nervous system. Gutstein's group reformulated imatinib using a simple, clinically approved carrier molecule called Captisol that markedly increased drug delivery to the brain.

"What's particularly exciting is that imatinib already is approved for use in humans, which suggests that we might be able to utilize this discovery to treat patients fairly soon," Gutstein said. He emphasized that the reformulated imatinib must first be tested for efficacy and safety in further animal studies, then in humans in a Phase I study.

Potential to reduce debilitating side effects

"Many patients in severe pain often refuse high doses of opioids because of the side effects, and they desperately need relief," Gutstein said. "We may be able to quickly translate this discovery and dramatically reduce the suffering endured by the sickest patients, and not just those with

cancer."

Patients taking morphine and other opioids can experience side effects ranging from unpleasant to life-threatening in their intensity, including itching, constipation, nausea and breathing depression. Reducing morphine tolerance could allow the use of lower doses to relieve pain with fewer side effects.

Provided by University of Texas M. D. Anderson Cancer Center