Methadone and Protease Inhibitor Interaction Called Into Question

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Protease inhibitors and methadone do not interact the way researchers long believed, according to a study in the March issue of the journal *Anesthesiology* and reported by ScienceDaily. The new findings suggest that recommended dose adjustments of methadone—a popular treatment for people in recovery from opiate drug use—for those undergoing antiretroviral therapy may not be required.

Protease inhibitors (PIs) have a profound effect on a liver enzyme called P450 CYP3A4, which is responsible for breaking down and helping the body eliminate dozens of different drugs. PIs suppress CYP3A4 levels to such a degree that there is not enough of the enzyme to break down other drugs, potentially causing toxic levels of co-administered medications to build up in the blood stream unless their doses are reduced.

Researchers have long assumed that CYP3A4 breaks down methadone, and current prescribing recommendations for PIs encourage providers to consider adjusting methadone doses accordingly. However, health care providers who prescribe methadone have reported unpredictable dosing problems with the drug.

To examine CYP3A4's influence on methadone, Evan Kharasch, MD, PhD, from the Washington University School of Medicine in St. Louis and his colleagues tested the two types of drugs in 12 HIV-negative patients. They found that methadone blood levels were completely unaffected by the combination of Norvir (ritonavir) and Crixivan (indinavir). In a second study, Kharasch's group tried dosing methadone with another PI, Viracept (nelfinavir), but found the same result. Viracept had no impact on methadone blood levels.

Because people taking methadone often take other drugs that influence the CYP3A4 enzyme—such as PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs)— these new data could have far reaching consequences. It is possible that many people have been receiving too little or too much methadone because their doses were adjusted based on suspected, but never confirmed, drug interactions. Kharasch says that research is ongoing. In the meantime, he is suggesting that companies that manufacture protease inhibitors reevaluate their prescribing recommendations regarding PIs and methadone.

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