Interactions between drugs can also be measured at lowest doses

April 11 2013

Clinical pharmacologists at Heidelberg University Hospital have achieved major progress for improving the reliability of drugs. In a pharmacological study, they showed for the first time that interactions between drugs can be detected with minute doses in the range of nanograms. However, at these low doses, the drugs are neither effective nor do they have side effects. This means that studies on interactions occurring in drug combinations can be conducted practically without posing risks or negative impacts on the participants. This is true not only for healthy volunteers, as has been observed to date, but also for patients. The study was published in the medical journal *Clinical Pharmacology & Therapeutics*.

"Many chronically ill or elderly patients today take several different drugs. Around two percent of all hospital stays in Germany are the result of interactions between the drugs," said Professor Walter E. Haefeli, Medical Director of the Department for Clinical Pharmacology and Pharmacoepidemiology at Heidelberg University, where the new technique of "nano-dosing" has been developed and tested. "Many interactions could be avoided if we were aware of them and took them into account."

Drug combinations rarely studied for interactions

However, very few drug combinations have been systematically tested for interactions to date. "Many risks remain unknown to date and need to

be studied," Prof. Haefeli explained. After initial tests conducted in animals, combinations are currentlybeing studied in healthy participants – with the usual therapeutic doses. Depending on the drug, this can strongly impact the body. Furthermore, a healthy person may react differently to a drug than a sick person does. This means that study findings can only be transferred to a limited extent.

Using mass spectrometry, an ultrasensitive technique, the team led by Prof. Haefeli succeeded in drastically reducing the dose for studies on interactions in study participants. Mass spectrometers are so sensitive that they are able to identify the drug in a single drop of blood. The scientists conducted a study on interactions in 12 healthy test persons taking the fungicide ketoconazole and the sedative midazolam simultaneously. For the study, they administered midazolamdoses of 0.0000001 g, which was 30,000 times lower than the amount used for therapy. Comparisons with higher doses revealed that the drugs behaved identically at all concentrations. Therefore, even a minimal concentration in the body is sufficient to reliably predict the extent of the interaction during normal use.

Inhibition of the liver enzyme measurable in the nanogram range

With the help of ultrasensitive mass spectrometers, the speed with which a drug is degraded can be measured. They are used wherever small amounts need to be detected in liquids, e.g., contamination in drinking water, doping agents or environmental toxins. To this end, a small amount of blood or other body fluid is withdrawn after certain time intervals in order to determine the remaining concentration of the drug. The mass spectrometer sorts the molecules and determines their concentration. Based on their characteristic properties, the drugs can be reliably identified. "For the first time, we have proven that with this

technique, we are able to find drugs in the blood even at extremely low doses, and that we can quantitatively determine them and identify their interactions," Prof. Haefeli said.

In the published study, the team investigated the interaction between the sedative midazolam, which is metabolized in the liver by the protein cytochrome P450 3A, and the fungicide ketoconazole, a well-known inhibitor of this cytochrome. The inhibition of the cytochrome and, in turn, the reduced degradation of midazolam, were already precisely measured in the nanogram dose. This interaction in particular plays an important role for patients who need to take several drugs simultaneously. Many drugs inhibit this enzyme, which metabolises around half of all regularly used medicines. However, if a drug is degraded too slowly, at normal doses, it accumulates in the body and, in the worst case, can cause toxicity.

Further studies planned

Prof. Haefeli and his team are now testing the new method in patients. "Since we can use minimal drug doses, these studies are also safe for patients," Prof. Haefeli explained. Heidelberg University pharmacologists will also examine the interactions of other medications that influence other metabolic enzymes. "The method could also be used in the many studies in which interactions are relevant for approval by the authorities, for instance," said Prof. Haefeli, looking toward the future.

More information: Burhenne J, Halama B, Maurer M, Riedel K-D, Hohmann N, Mikus G, Haefeli WE: Quantification of femtomolar concentrations of the CYP3A substrate midazolam and its main metabolite 1'-hydroxymidazolam in human plasma using ultra-performance liquid chromatography coupled to tandem mass spectrometry. *Anal Bioanal Chem* 2012;402:2439-50.

Medical Xpress

Halama B, Hohmann N, Burhenne J, Weiss J, Mikus G, Haefeli WE: A nanogram dose of the CYP3A probe substrate midazolam to evaluate drug interactions. *Clin Pharmacol Ther*; accepted article preview online February 8, 2013; doi:10.1038/clpt.2013

Provided by Heidelberg University Hospital

Citation: Interactions between drugs can also be measured at lowest doses (2013, April 11) retrieved 19 April 2024 from https://medicalxpress.com/news/2013-04-interactions-drugs-lowest-doses.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.