Research helps explain links between antibiotic use and heart attack risk

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University of Dundee research has helped explain why a commonly used antibiotic can lead to an increased risk of heart attacks, opening up the possibility of precision prescribing based on a patient's genes.

Clarithromycin accounts for around 15% of all primary care antibiotic prescriptions in the UK and is recommended for treatment of patients with chest infections. In recent years it has been suggested that patients taking clarithromycin rather than alternative antibiotics were more likely to suffer a serious cardiovascular event, but research into this association had proved inconclusive.

In order to provide greater clarity, the Dundee team, led by Dr. Ify Mordi from the University's School of Medicine, took a different approach to previous studies. Taking advantage of the extensive electronic database compiled locally, they explored both medical prescribing records and genetic data to determine whether clarithromycin use was indeed linked to an increased risk of heart problems.

Their study showed that, compared to patients prescribed amoxicillin, those taking clarithromycin were 31% more likely to be admitted to hospital with a heart problem within 14 days of starting the prescription and 13% more likely to be admitted to hospital with a heart problem up to a year after the conclusion of the prescription.

In addition, they found that patients also taking certain types of medications, such as statins, at the same time were even more likely to have a heart issue if given clarithromycin rather than amoxicillin.

Medications such as statins and clarithromycin work in the body using a pathway controlled by a protein called P-glycoprotein. Using genetic data, the researchers found that patients with a genetic predisposition to lower P-glycoprotein activity were also at 40% higher risk of heart problems up to a year after prescription when taking clarithromycin rather than amoxicillin.

Taken together, these results suggest that patients should be prescribed

alternative antibiotics if they are taking P-glycoprotein inhibitors such as statins, or if they have a particular genotype.

"Studies into the association between clarithromycin with cardiovascular events had been conflicting but we knew it was possible that any risk would be partly mediated through drug-drug interactions and only evident in at-risk populations," said Dr. Mordi.

"We set out to examine whether this association might be mediated via P-glycoprotein, a major pathway for clarithromycin metabolism. One issue with this type of analysis is it may be biased in that people who are taking statins, for example, are more likely to have had a heart problem before, and so are more likely to have heart issues in future. In Tayside we have a wonderful genetic resource which can take out this bias, as you can change your prescription, but not your genes."

In addition to examining anonymised medical records for adult patients prescribed either clarithromycin or amoxicillin in Tayside between 2004 and 2014, Dr. Mordi and his colleagues conducted a genomic observational cohort study evaluating genotyped patients from the GoDARTS database of 18,306 individuals recruited in the same area between 1989 and 2015.

Dr. Mordi continued, "We found that clarithromycin use was associated with an increased risk of cardiovascular hospitalization up to a year post-prescription compared to amoxicillin. There appears to be an effect modification via P-glycoprotein, and these results may have implications for clarithromycin use in patients taking P-glycoprotein inhibitors or with low genetically-predicted P-glycoprotein activity."

The paper is published today in *PLOS Medicine*.

More information: Ify R. Mordi et al. Genetic and pharmacological

relationship between P-glycoprotein and increased cardiovascular risk associated with clarithromycin prescription: An epidemiological and genomic population-based cohort study in Scotland, UK, *PLOS Medicine* (2020). DOI: 10.1371/journal.pmed.1003372

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