23rd January 2020

Sticky “last line of defence” antibiotic provides glue for successful treatment

Researchers have found how an antibiotic used to treat a debilitating gut infection stays put inside the body giving it time to effectively treat the problem, a discovery that will pave the way for the development of more effective antibiotic treatments to fight superbugs.

PE (pseudomembranous colitis) is a debilitating inflammation of the colon caused by infection with the nasty microbe *Clostridium difficile* (and sometimes *Staphylococcus aureus).* The sugar- or carbohydrate-containing antibiotic known as vancomycin is taken by mouth to kill it.

To be effective, vancomycin needs to stay in the GI tract (gut) close to where it is needed and not be diluted away or lost through the gut lining & into the bloodstream. A multi-disciplinary team of scientists at the Universities of Nottingham and Leeds have now shown this ‘staying put’ mechanism is precisely what happens and that it can occur in an unexpected way.

Forming a formidable barrier

The research, pubished today (23/24 January) in Nature’s *Scientific Reports* shows that protein-carbohydrate molecules of the mucus lining the gut called **mucins** provide a formidable barrier helping to prevent the drug escaping using a unique mechanism of formation of large molecular complexes or clumps. The antibiotic and mucins join together to form a mucoadhesive complex, trapping the antibiotic within large complexes. It is the trapped vancomycin which the scientists believe may lead to delayed transit of the antibiotic leading to prolonged exposure of the antibiotic to the particularly nasty and infectious *C. difficile.*

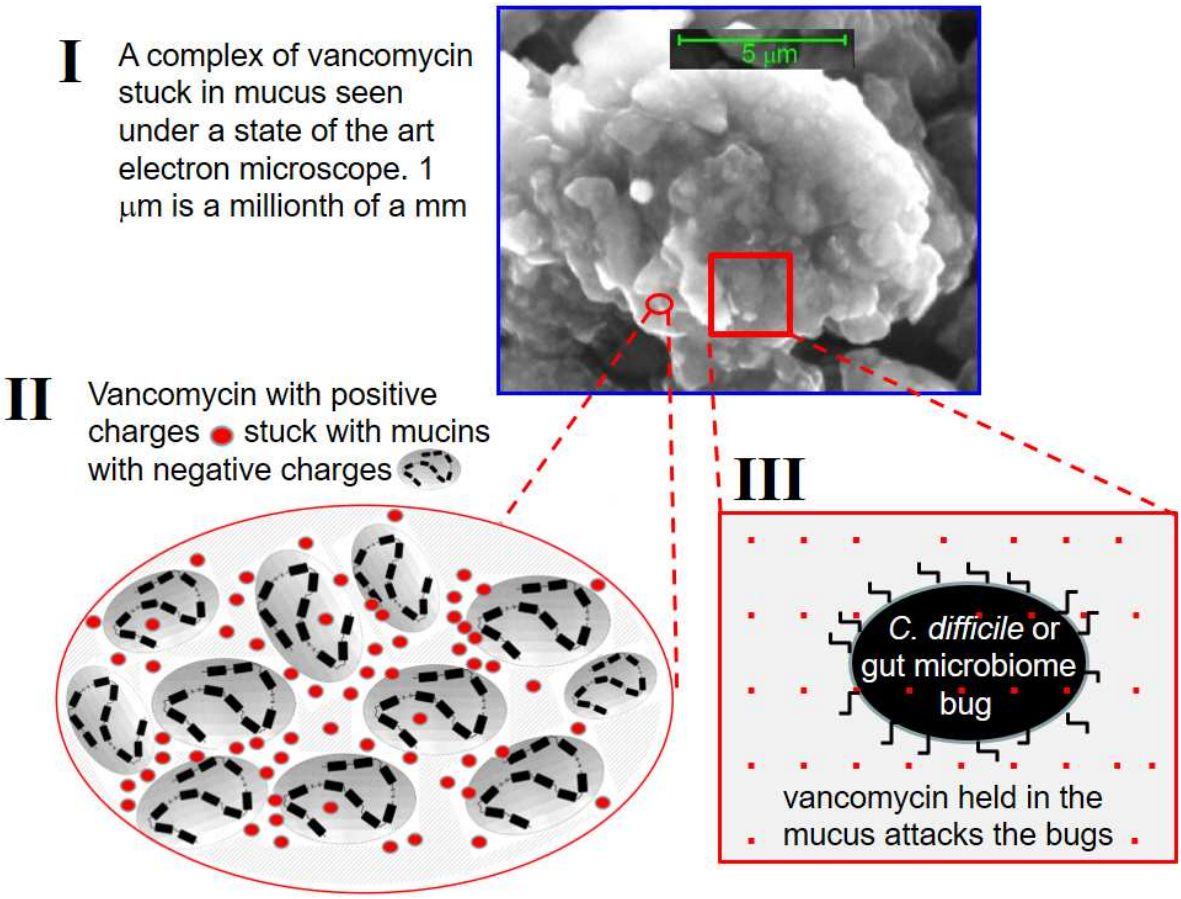
Dr Mary Phillips-Jones, Associate Professor in Polymer & Microbial Biophysics at the University of Nottingham led the research, she said: “Vancomycin is a precious ‘last-line’ antibiotic in the clinician’s arsenal of therapies to fight several important pathogens including MRSA, pneumonia, as well as *C. difficile.* The clumping effect with gut mucins revealed in our study not only gives new information about what may happen when the antibiotic is given orally, but might also provide new insights into its behaviour when infused into patients suffering from other life-threatening infections”

The findings also fit with other studies which show that vancomycin pills or capsules produce high levels of vancomycin resistance amongst some gut bacteria (VRE), contributing to the generation of antimicrobial resistance (a serious concern); the clumping/ complexation phenomenon may therefore provide the first explanation of a mechanism by which this VRE generation occurs. But the benefits of taking vancomycin at the right time and when appropriate still outweigh any negative generation of antimicrobial resistance, and the study highlights that it is wise to take vancomycin when your GP advises it is good to do so.

Steve Harding, Professor of Biochemistry added: “The antibiotic vancomycin is a truly remarkable molecule or “supermolecule” – a drug with its own mucoadhesive or sticky property which slows its transit through the gut right down giving maximum therapeutic effect and minimizing the amount of unused vancomycin being returned to the environment which can have bad consequences. If scientists are going to win the fight against anti-microbial resistance, teamwork like this successful one are going to prove crucial.”

Cartoon Pic:

Supermolecules versus Superbugs



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More detailed Caption

Vancomycin is taken to combat pseudomembranous colitis (caused by *Clostridium difficile* and occasionally by other microbes including *Staphylococcus aureus*) and is taken through the mouth. Its interactions with mucins from the mouth, stomach and intestine have been studied using sophisticated biophysical analyses, namely analytical ultracentrifugation, dynamic light scattering and environmental scanning electron microscopy. Panels I and II: Vancomycin (carrying a net positive charge) is shown to have strong mucoadhesive properties with mucins (carrying negative charges), with the largest complexes (up to 20 μm) formed with stomach and intestinal mucins. Panel III: the vancomycin-mucin mucoadhesive matrix may provide a more efficient mechanism for combatting disease-producing bacteria such as *C. difficile* than hitherto anticipated, perhaps retaining vancomycin in closer proximity with mucus-trapped microbes for longer than expected. If so, this could provide useful information about how to implement the increasingly popular practice of intracolonic administration of vancomycin. However, suggested close contact of vancomycin with other members of the gut microbiome may also lead to an increased incidence of antimicrobial resistance to the antibiotic.

LINK TO THE PAPER: https://rdcu.be/b0CA2

More information on the research is available from Dr Mary Phillips-Jones at the University of Nottingham on Mary.Phillips-Jones@nottingham.ac.uk