INFECTION

New vaginal drug delivery methods

Women are more susceptible to sexually transmitted infections (STIs) than men, yet effective female-controlled prevention methods remain elusive.

Two new studies report novel techniques for the effective delivery of antimicrobial agents to the vagina. The first study reports development of aciclovir-based nanoparticles that can penetrate vaginal mucus to provide protection against herpes simplex virus 2 (HSV-2); the second describes the use of a polycaprolactone matrix for sustained release of ciprofloxacin and miconazole into vaginal fluid.

The first study comes from a research team in Baltimore, USA, who previously developed mucus-penetrating particles (MPPs) that can move through human cervicovaginal mucus more efficiently than conventional polymeric nanoparticles (CPs), which tend to get trapped in the superficial luminal mucus layer. Here, the researchers studied fluorescently labelled MPPs in a mouse model to assess their distribution, retention and toxicity in the vagina. They found that MPPs travelled by advection, penetrating ~100 µm of mucus in 10 min, a distance that would take about 4 h to traverse via diffusion. Quantification of the fluorescence on vaginal and ectocervical tissue revealed that MPPs provided near complete coverage of the epithelial surface, while CPs covered only 30–36% of tissue. “We also found that MPPs were as safe as placebo gel after daily administration for 1 week,” says Laura Ensign, lead author of the study.

These positive findings led the investigators to create nanoparticles composed of aciclovir monophosphate, which they found were significantly more protective against HSV-2 infection than soluble drug (infection rates 46.7% versus 84%; $P=0.002$). Even at 10 times the concentration of MPPs, soluble drug was considerably less protective against HSV-2.

“Our next move is to show that MPPs are safe for vaginal administration in humans,” says Ensign. “MPP technology could lead to a once-daily treatment for prevention of STIs, for contraception, and for treatment of female reproductive tract disorders.” The effect of pH changes, bacterial flora, and the presence of semen will all have to be taken into account before this technology can be successfully transferred to humans.

For the second study, Allan Coombes and colleagues at the University of Queensland, Australia, tackled vaginal STI treatment from a slightly different angle. Based on the reported disadvantages of gels and creams (difficult to apply, poorly retained, short duration of drug release), researchers instead utilized silicone elastomer intravaginal inserts, traditionally used to provide sustained drug release for estrogen replacement therapy and contraception. “We have been developing microporous polymeric matrices for several years for applications in tissue engineering and controlled drug delivery,” says Coombes. “Application in vaginal delivery was a logical extension of this work and now forms a major part of my group’s research activities.”

Coombes and his team found that polycaprolactone matrices could be loaded with ciprofloxacin (a potent bactericide used to treat gonorrhoea) to concentrations of up to 15% w/w, while miconazole (an antifungal agent for treatment of yeast infections) could be loaded up to 1–3%. Drug release kinetics, measured in simulated vaginal fluid, revealed sustained release for both ciprofloxacin (30 days) and miconazole (13 days). Predicted *in vivo* release concentrations were found to be much higher than the minimum inhibitory concentrations of both drugs for most STIs.

“We are currently applying our approach to a variety of antiviral drugs, including tenofovir and nevirapine for the prevention of HIV transmission,” says Coombes. “The versatility of our materials enables us to incorporate combinations of drugs, which are an accepted part of future strategies to combat viral and bacterial infections.”

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Original articles Ensign, L. M. *et al.* Mucus-penetrating nanoparticles for vaginal drug delivery protect against herpes simplex virus. *Sci. Transl. Med.* 4, 138ra79 (2012) | Dang, N. T. *et al.* Development of intra-vaginal matrices from polycaprolactone for sustained release of antimicrobial agents. *J. Biomater. Appl.* doi:10.1177/0885328212437393