Pharmacokinetic and Pharmacodynamic Evaluation of IQP-0528 Quick-Dissolving Films in Macaques as an HIV Microbicide

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Purpose

Providing several dosage forms of potent HIV microbicides for women has the potential to improve product adherence in pre-exposure prophylaxis trials. Microbicide delivery through solid dosage forms such as quick-dissolving polymeric films may be more acceptable to women than gels because of their small size, no need for an applicator, easier storage and transport, and increased product stability. We evaluated the pharmacokinetics and pharmacodynamics of unencapsulated and nanoparticle-encapsulated vaginal film formulations of the non-nucleoside reverse transcriptase inhibitor IQP-0528 in pigtailed macaques.

Methods

Polyvinyl alcohol based vaginal IQP-0528 films (1.5% w/w- 450 µg, 22x44x0.1mm, surface area 75% of a human dose) with and without nanoparticles [encapsulation into poly(lactic-co-glycolic acid)] were inserted into pig-tailed macaques (n=9 for each group). Blood, vaginal pH measurements, cervicovaginal lavage, and vaginal spears were collected before, and up to 24 hours after film application. Vaginal biopsies were also collected from macaques at 24 hours. IQP-0528 was quantitated in plasma, vaginal fluid collected at 0, 1, 4, 24 hours, days 7, 14, and 23 by LC-MS/MS. The drug was also quantitated in vaginal and rectal biopsies (24 hours). Anti-viral activity was tested ex vivo by co-culturing vaginal tissues with activated human peripheral blood mononuclear cells (PBMC).

Results

Median macaque vaginal fluid concentrations of IQP-0528 obtained at 1, 4, and 24 hours post film application were 160.97, 181.79, and 484.50 µg/mL, respectively. Median vaginal tissue IQP-0528 concentrations at 24 hours were 3.82 µg/g with similar concentration values measured proximal, medial and distal to the cervix. In vaginal tissue and secretions the nanoparticle formulation was similar to the base formulation. A single application of either formulation did not disturb the vaginal microflora or the pH (7.24±0.84) or cause a significant change in the pro-inflammatory cytokines. The IQP-0528 vaginal film formulations resulted in high mucosal concentrations of IQP-0528 1 - 5 logs higher than the *in vitro* IC_{90} (0.146 µg/mL). IQP-0528 extracted from vaginal tissues obtained from macaques at necropsy protected co-cultured PBMC from HIV-1 infection, with a viral inhibition range of 90-100%. Anti-viral activity was observed in vaginal tissues that were proximal, medial, and distal relative to the cervix. Viral inhibition was not detected in baseline tissue samples.

Conclusion

The rapidly obtained levels and excellent coverage suggest that the films may be protective in vaginal repeated low-dose SHIV transmission studies and warrant further evaluation.