559b

INTERNATIONAL PARTNERSHIP for MICROBICIDES
8401 Colesville Road, Suite 200, Silver Spring, MD 20910 USA
Tel: 301-608-2221, +27 21 860 2300 -- Fax: 301-608-2241, +27 21 860 2308
Email: anel@ipm-microbicides.org

Safety and Pharmacokinetic Assessment of 28 Day Anti-HIV Dapivirine Intravaginal Microbicide Rings

Annalene Nel[1], Shanique Smythe[1], Katherine Young[1], Karl Malcolm[2], Zeda Rosenberg[1], Joseph Romano[1] (1) International Partnership for Microbicides, Silver Spring, MD 20910, US; (2) Queen's University, Belfast, Northern Ireland

Abstract

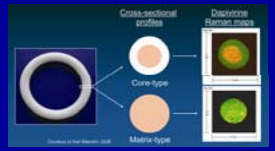
Background: Dapivirine (TMC 120) is a non-nucleoside reverse transcriptase inhibitor in development as a microbicide for prevention of HIV transmission. Formulation of dapivirine in intravaginal rings (IVRs) for 28 day use represents a potential means of increasing microbicide product adherence and efficacy.

Methods: Dapivirine (25 mg) was incorporated into either matrix (drug dispersed evenly throughout) or in reservoir (drug localized to an inner core inside an unmedicated outer sheath) IVRs. Placebo rings were matrix type with no drug. A 24 participant, phase I, double-blind, randomized (1:1:1), placebo-controlled 28 day study was conducted in a single centre to evaluate delivery of dapivirine (plasma levels, vaginal fluids, pharmacokinetic parameters), and to assess local and systemic safety. Dapivirine levels were evaluated from plasma and vaginal fluid samples collected at sequential time points over a 24-hour period on Day 1 (post insertion) and Day 28 (post removal) and at sequential time points over a 33-day (28-day treatment; 5-day follow-up) period. Safety measurements were monitored over 33-day period.

Results: Dapivirine concentrations were considerably higher for matrix than for reservoir rings during the entire 33 day period. Dapivirine concentrations were 73 times (plasma), 370 times (vaginal fluid, area of the ring), 610 times (vaginal fluid, at the cervix) and 195 times (vaginal fluid, area of the introitus) higher for matrix rings on day 1 of treatment. Differences in mean dapivirine concentrations between the two ring types decreased over the 28 days of use. Distribution throughout genital tract was comparable with both rings. Systemic exposure to dapivirine was low, not exceeding 2ng/ml. A rapid increase in plasma concentrations was seen immediately after matrix ring insertion with mean peak concentrations observed 24 hours post ring insertion. None of the AEs reported were considered to be definitely or probably related to study treatment. Findings considered to be possibly related to intravaginal ring treatment were not different for the three treatment groups. No clinically relevant changes occurred compared to baseline. No serious or drug-related treatment-emergent AEs were reported.

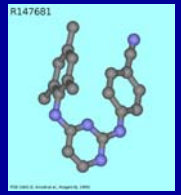
Conclusions: Different dapivirine IVR types were safe and well tolerated in healthy HIV-negative women. Pharmacokinetic data supports future development of dapivirine intravaginal rings as a monthly administered microbicide.

Intravaginal Ring (IVR) Structures



- Tin catalyzed silicone elastomer composition
- Matrix IVR: 25 mg dapivirine dispersed evenly throughout ring
- Reservoir IVR: inner core containing 25 mg dapivirine surrounded by unmedicated outer sheath
- Placebo rings were matrix type without drug
- Outer diameter 56 mm
- Weight approximately 9 grams

Dapivirine: A Potent NNRTI



- Dapivirine is in development as a microbicide gel and intravaginal ring (IVR) for prevention of HIV transmission
- EC_{50} of 0.3 ng/mL and EC_{90} of 0.9 ng/mL against HIV-1
- Potent antiviral activity against HIV-1 including strains with NNRTI-resistance mutations

Study Objective

To evaluate the feasibility of using matrix and reservoir IVRs containing 25 mg dapivirine to deliver drug for 28 continuous days

- Safety and tolerability vs. placebo
- Plasma concentrations
- Concentrations in vaginal fluids

Study Design

- Double-blind, placebo controlled trial conducted at a Phase 1 unit in Belgium
- 24 healthy, HIV-negative women 18 to 35 years of age
- 1:1:1 randomization to 25 mg matrix IVR, 25 mg reservoir IVR, or placebo IVR (n=8 in each group)
- Pelvic/colposcopic examinations performed, adverse events assessed, and subject-reported genital symptoms documented at each study visit
- Hematology, liver and renal function, and urinalysis done at screening and final visit
- Blood samples and vaginal fluid samples (near IVR, cervix, introitus) collected at the indicated time points:

Timeline of Study Events (IPM018)

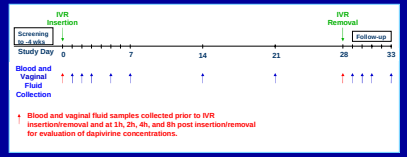


Table 1. Number and Percentage of Subjects with Treatment-Emergent Adverse Events*

Adverse Event	Matrix IVR (25 mg) N=8 n (%)	Reservoir IVR (25 mg) N=8 n (%)	Placebo IVR N=8 n (%)	Total
Any event	7 (87.5)	8 (100)	8 (100)	23 (95.8)
Headache	4 (50)	4 (50)	5 (62.5)	13 (54.2)
Vaginal hemorrhage	3 (37.5)	2 (25)	2 (25)	7 (29.2)
Abdominal pain	1 (12.5)	2 (25)	3 (37.5)	6 (25)
Fatigue	1 (12.5)	2 (25)	3 (37.5)	6 (25)
Lower abdominal pain	0	0	3 (37.5)	3 (12.5)
Diarrhea	1 (12.5)	2 (25)	0	3 (12.5)
Nausea	1 (12.5)	1 (12.5)	1 (12.5)	3 (12.5)
Vaginal/genital discharge	1 (12.5)	1 (12.5)	1 (12.5)	3 (12.5)
Allergy to arthropod bite	0	1 (12.5)	1 (12.5)	2 (8.3)
Nasopharyngitis	0	1 (12.5)	1 (12.5)	2 (8.3)
Back pain	1 (12.5)	0	1 (12.5)	2 (8.3)
Breast tenderness	1 (12.5)	1 (12.5)	0	2 (8.3)
Metrorrhagia	2 (25)	0	0	2 (8.3)
Vulvovaginal discomfort	1 (12.5)	0	1 (12.5)	2 (8.3)

* Events that occurred in ≥2 subjects are shown.

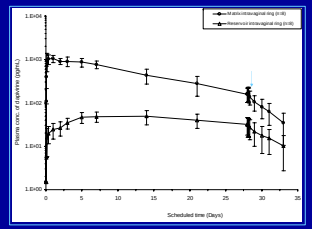
Table 2. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Assessed as Possibly Related to IVR

Adverse Event	Matrix IVR (25 mg) N=8 n (%)	Reservoir IVR (25 mg) N=8 n (%)	Placebo IVR N=8 n (%)	Total
Headache	3 (37.5)	3 (37.5)	3 (37.5)	9 (37.5)
Vaginal/genital discharge	1 (12.5)	1 (12.5)	1 (12.5)	3 (12.5)
Fatigue	0	2 (25.0)	1 (12.5)	3 (12.5)
Abdominal pain	0	1 (12.5)	2 (25.0)	3 (12.5)
Nausea	0	1 (12.5)	1 (12.5)	2 (8.3)
Candidiasis	1 (12.5)	0	0	1 (4.2)
Vulvovaginal pruritus	1 (12.5)	0	0	1 (4.2)
Vulvovaginal discomfort	1 (12.5)	0	0	1 (4.2)
Bacterial vaginitis	0	1 (12.5)	0	1 (4.2)

Safety Results

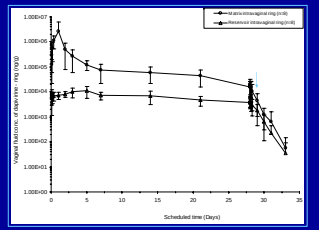
- 25 mg matrix and 25 mg reservoir IVRs were safe and well tolerated in healthy, HIV-negative women
- No clinically relevant changes from baseline were noted in any group
- No AEs were considered definitely or probably related to the IVR
- AEs considered to be possibly related to the IVR were not different for the three study groups (Table 2)
- Number of grade 1 and 2 AEs was similar among the three study groups
- One grade 3 AE, headache, occurred in the matrix IVR group on Day 1 with a duration <24 hours

Figure 1. Mean Plasma Concentrations of Dapivirine Released from IVRs Over 28 Days*



* ↓ indicates IVR removal at Day 28

Figure 2. Mean Concentrations of Dapivirine in Vaginal Fluids at the IVR Site Over 28 Days*

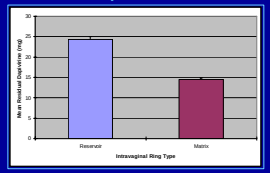


* ↓ indicates IVR removal at Day 28

Plasma Concentrations of Dapivirine

- Plasma concentrations were low with both types of IVR, but higher with the matrix than reservoir IVR (C_{max} 1.21 ng/mL and 0.05 ng/mL, respectively)
- Individual plasma concentrations did not exceed 2 ng/mL
- Dapivirine was detectable in plasma of all subjects at 1 hour and 4 hours post insertion of the matrix and reservoir IVRs, respectively
- Peak mean plasma concentrations were reached at 24 hours post insertion with the matrix IVR and at 120 hours post insertion with the reservoir IVR (t_{max} 7.89 h and 252.8 h, respectively)
- Rates of plasma elimination post IVR removal were similar for the two ring types
- Mean terminal half-life of dapivirine in plasma was 64 hours and 83 hours for the matrix and reservoir IVRs, respectively

Figure 3. Residual Dapivirine Content in IVRs after 28 Days of Use



- IVRs were removed from study subjects on Day 28, rinsed with sterile water, and autoclaved
- Rings were cut into small sections, extracted into solvent, filtered, and analyzed by reverse-phase HPLC/UV for dapivirine content
- On average, more dapivirine remained in reservoir IVRs (97%) than matrix IVRs (58%) after 28 days of use

Dapivirine Concentrations in Vaginal Fluids Near the IVR:

- Higher concentrations observed with matrix than reservoir IVR
- Dapivirine was detectable in cervicovaginal fluids of all subjects at 1 hour post insertion of the matrix and reservoir IVRs
- With matrix IVR, mean peak at 24 hours post insertion vs. mean peak at 5 days with reservoir IVR (t_{max} 23.8 h and 119.3 h, respectively)
- C_{max} values were 2.87 mg/g for the matrix IVR and 0.01 mg/g for the reservoir IVR
- For both IVR types, concentration-time curves for the cervix and introitus were similar to those for the area near the IVR, although the values were slightly lower
- Mean terminal half-life of dapivirine in vaginal fluids ranged from 15-16 hours with both IVRs at all three sample sites

Summary and Conclusions

- Both matrix and reservoir IVRs containing 25 mg dapivirine were safe and well tolerated in healthy HIV-negative women for 28 days
- Dapivirine was effectively distributed throughout the cervico-vaginal area at concentrations 16,000-fold (reservoir IVR) to 3 million-fold (matrix IVR) greater than the EC_{90} against HIV-1
- Dapivirine concentrations in plasma were very low (<2ng/mL); >1000-fold less than plasma concentrations at the maximum tolerated oral dose
- Pharmacokinetics and safety data support the future development of dapivirine IVRs as a monthly dosed microbicide

Acknowledgement:
Investigators and Personnel of Drug Research Unit, UZ Ghent, De Pintelaan 185, 9K4 9000 Ghent, Belgium and IPM Clinical affairs team.