Poster #1000

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Sustained Delivery of Microbicide Dapivirine Using Intra-vaginal Rings: An Independent Clinical Assessment of Safety & Drug Delivery in Women

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ABSTRACT

BACKGROUND: Vaginal Microbicides for the prevention of HIV transmission may be an important option for protecting women from infection. Intra-vaginal rings (IVR) are one approach to sustained release of microbicides that could provide increased flexibility for the user and increased product adherence. This report describes two independent phase I safety trials designed to evaluate delivery of the NNRTI microbicide dapivirine from IVR.

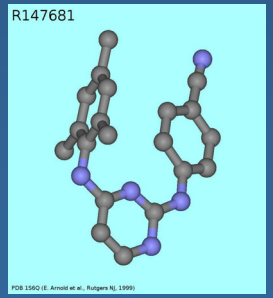
METHODS: Each study involved a differently designed silicone elastomer core type IVR. Study 1 used IVR with 120 mg or 0 mg (placebo) of dapivirine in a cross-over design involving 12 sexually abstinent healthy volunteers. Each participant underwent 7 days of placebo then 7 days of dapivirine ring use. Study 2 was a randomized, double blind placebo controlled study involving 7 day use of IVR with 25 mg (10 women) or 0 mg of dapivirine (3 women). Safety, tolerability, and drug distribution were assessed similarly in each study.

RESULTS: All participants completed both studies. Safety was assessed in each study by measurement of clinical laboratory parameters, adverse events, and pelvic examinations. There were no deaths, serious adverse events, or adverse events (AE) resulting in study discontinuation in either trial. Similar AE were observed in the placebo and treatment groups of both studies. IVR in each study were found to be generally safe and well tolerated. Drug levels in different sample types collected on day 7 allow summary comparison between studies. Levels in vaginal fluids (Sno-strip collection) and in cervical and vaginal tissues (biopsy) at day 7 were compared at the cervix, introitus, and the vaginal ring areas. In study 1, mean vaginal fluid levels ranged from ~17 ng/strip (cervix) to ~74 ng/strip (ring area); mean tissue levels ranged from ~279 ng/gm (introitus) to ~703 ng/gm (ring area). In study 2, mean fluid levels ranged from 7 ng/strip (cervix) to ~94 ng/strip (ring area); mean tissue levels ranged from ~680 ng/gm (cervix) to 2480 ng/gm (ring area). Mean plasma levels in each study were <50 pg/mL.

CONCLUSIONS: Two IVR delivery systems with different amounts of dapivirine were found to be generally safe and well tolerated in independent clinical trials. Both IVR delivered dapivirine throughout the genital tract although tissue levels were higher in study 2. Both studies suggest IVR delivery of microbicides merits further study.

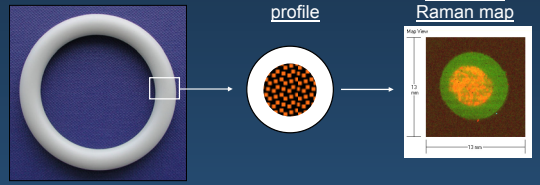
*Note: Tissue data from the second study presented here is revised relative to the original abstract

DAPIVIRINE: A POTENT NNRTI



DAPIVIRINE is an NNRTI developed originally as a therapeutic; 11 clinical studies were conducted via oral administration; it is a highly potent ARV, non-mutagenic, non-teratogenic with low cytotoxicity.

INTRAVAGINAL RING DELIVERY



- Attractive Technology: (1) >30day use (2) Ease of use / Higher Compliance (3) Inexpensive (4) An approved technology for multiple indications
- Ring Structure: Silicone elastomer composition- Medicated core within control-release outer sheath.

CLINICAL STUDY OBJECTIVES/DESIGN

Objectives:

(1) Determine safety and tolerability of 7 day dapivirine IVR use; (2) Determine vaginal fluid/tissue and plasma levels of dapivirine.

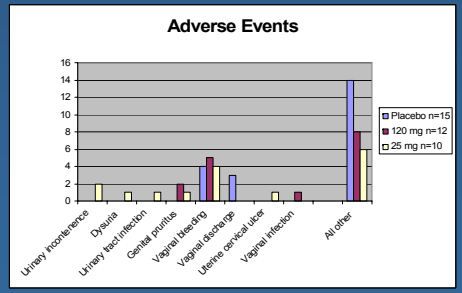
Design:

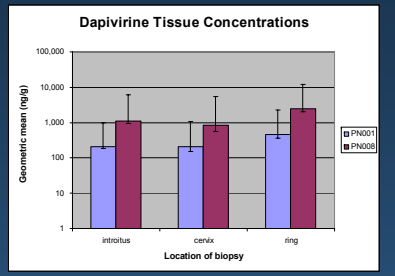
PN001: two-core ring design (120 mg dapivirine); cross over design (placebo/treatment), 12 sexually abstinent 18-50 year old women

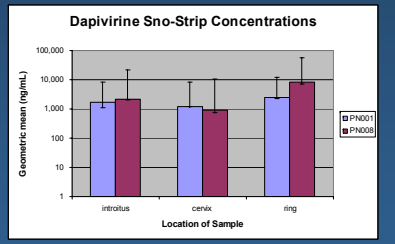
PN008: Full length single core design (25 mg dapivirine); double-blind, randomized, placebo controlled; 13 sexually abstinent 18-50 year old women (3 placebo/10 treatment).

STUDY RESULTS

Adverse Event	Placebo	120 mg	25 mg
Number of women	15	12	10
CNS	3	1	2
Eye	0	1	0
Cardiac Disorder	1	0	0
GI System	6	2	0
General Disorder	1	3	3
Musculoskeletal System	1	0	0
Respiratory System	1	1	0
Injury, poisoning, procedure comps	0	0	1
Skin/sub-Q tissue	1	0	0
Renal/Urinary Disorder	0	0	4
Urogenital System	7	8	6
TOTAL	21	16	16







SUMMARY AND CONCLUSIONS

- Dapivirine was safe and well tolerated when delivered intravaginally using two ring formats, for 7 days
- Levels of dapivirine in vaginal fluids and tissues were >1000X the EC_{50}, and distribution was comparable with each IVR
- IVR technology is appropriate for vaginal delivery of microbicide candidates and should be evaluated further.