Population PK Modeling of Dapivirine Released from Vaginal Rings

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Introduction

Dapivirine is a non-nucleoside reverse transcriptase inhibitor with potent antiviral activity against HIV-1. The International Partnership for Microbicides (IPM) has developed a vaginal ring containing dapivirine (25 mg) for use as a microbicide to protect women against HIV infection through sexual intercourse. These rings are placed in the upper third of the vagina where they slowly release the active drug. In two studies IPM 013 and IPM 024 vaginal fluid concentrations of dapivirine were collected from the area of the introitus and cervix by means of tear test strips. These data were analyzed simultaneously by a population PK approach. The analysis was based on 951 samples originating from 41 healthy, HIV-1 negative women.

Objectives

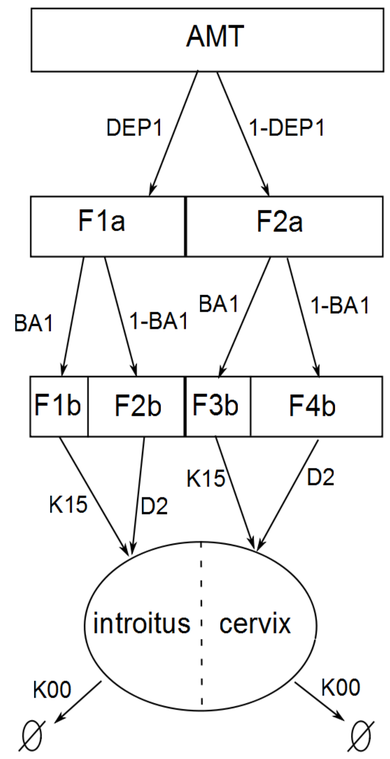
A population PK model was built to describe the time course of vaginal fluid levels of dapivirine at the introitus and cervix in order :

- to predict the drop in vaginal fluid concentrations of dapivirine after various intervals of ring removal;
- to predict vaginal fluid concentrations of dapivirine when the rings are inserted successively every four weeks.

Assumption: The pharmacokinetic of dapivirine is independent of the place of sample measurements (introitus/cervix).

PK model

- Distribution of dapivirine to the introitus and cervix is described by a combined first and zero order release process
- Differences in the vaginal fluid concentrations of dapivirine at the cervix and introitus are described by two different fractions of amount reaching the sampling sites.



Implementation in NONMEM

- AMT: total amount of dapivirine which is contained in the vaginal ring.
- F1a, F2a: fractions of AMT ultimately distributed to introitus and cervix, respectively, determined by DEP1
- F1b, F2b: fraction of F1a which is released from the ring via a first and zero order process, respectively, determined by BA1; (similar for F3b and F4b)
- K15: first order release rate constant
- D2: wearing period of a ring (in hours)
- K00: first order elimination rate constant

Software

Non-linear mixed effects modeling was performed using NONMEM (v7.1, Method FOCE INTER) with gfortran (v4.5.0) together with PSN (v3.1.0) and R (v2.11.1).

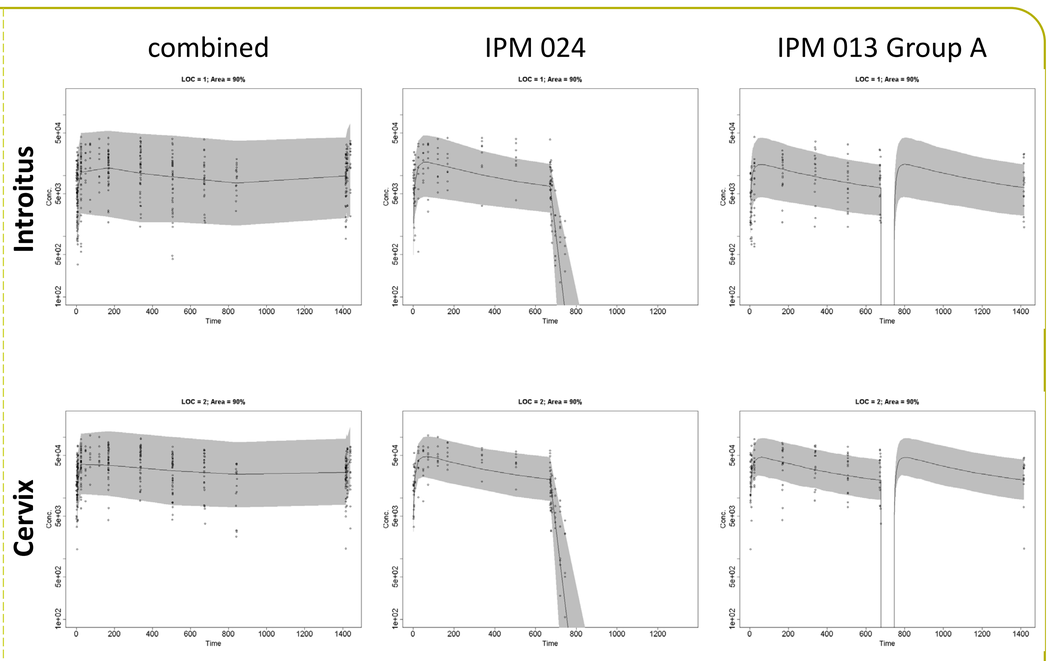
Results

- Inter-individual variability (IIV) was detected for each parameter except for BA1
- Fixed effects parameters could be estimated with high precision (CV<18%)
- Except for IIV(V) (CV=60.4%) random parameters were estimated with good precisions (CV<42%)
- Model predicts that concentration at the cervix is around three times higher than concentration at the introitus
- Around 60% of drug release occurs by a first order process
- Beside a slight bias due to lack of data in the initial phase, diagnostic plots showed no substantial bias
- VPCs showed that observed concentrations during the ring wear and washout periods are predicted well

Parameter	Estimate	IIV
K00 [h^{-1}]	0.0649	0.132
V [g]	10.9	0.0915
BA1 [0,1]	0.580	0 FIX
DEP1 [-∞,+∞]	-1.04 (0.261)*	0.180
K15 [h^{-1}]	0.00265	0.0883
Ω(DEP1,K15)	-	-0.0929
σ1 (introitus)	0.561	-
σ2 (cervix)	0.350	-

*DEP1 on a linear scale

Final estimates of the fixed and random parameters. Ω(.,.) denotes the covariance between the respective parameters, and σi denotes the variance of the residual error at the two sample sites.



Grey shaded bands indicate concentration regions in which 90% of the simulated concentration values are contained. Solid lines indicate calculated medians, and circles display measured concentration values. Drops in figures in the bottom row indicate vaginal lavage.

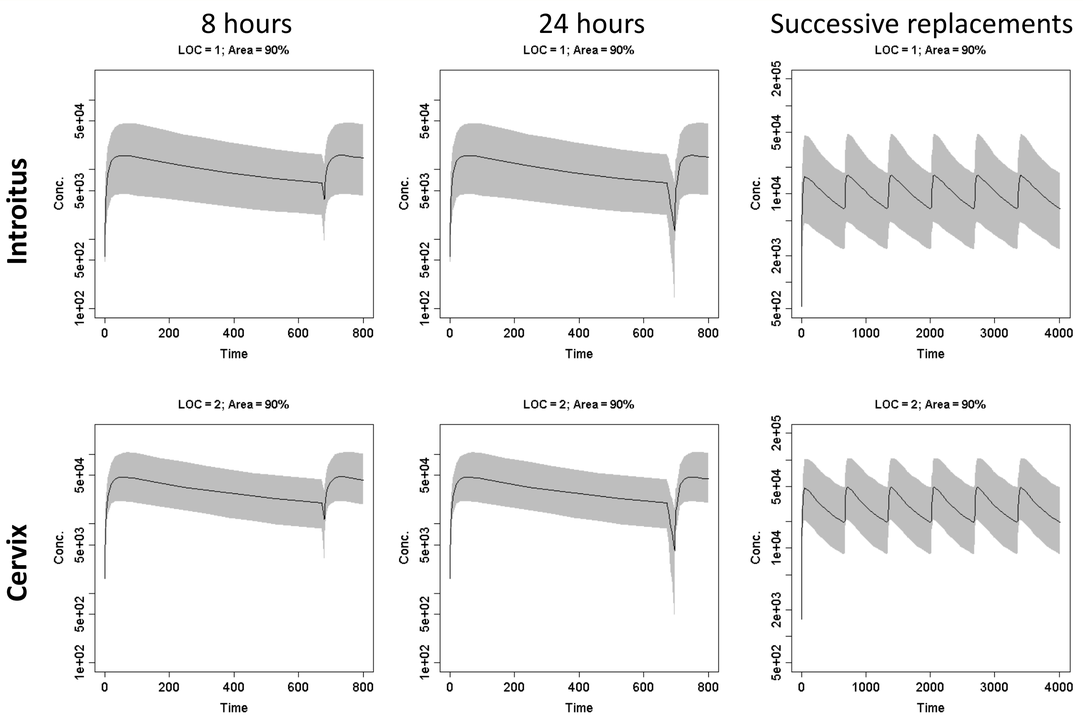
Simulations

In order to investigate the effect of removing a ring for a certain time interval different scenarios were simulated in which a ring was removed for 8, 12 and 24 hours after a wearing time of 28 days. The drop in median concentrations at the introitus and cervix are listed in the table on the right hand side.

- Vaginal fluid concentrations dropped to a value of about 60, 45, and 20% of the level prior to ring loss at 8, 12, and 24h after removal, respectively
- Simulation of successive replacements of vaginal rings every 28 days showed virtually no accumulation in vaginal fluid levels

-After a wearing period of 4 weeks the contribution of the first order release process is negligible ($T_{1/2}$ around 11 days)

- Steady state concentrations are mainly determined by the zero order release process



Drop in median vaginal fluid concentrations of dapivirine at the introitus and cervix after a ring was worn for 28 days and removed for 8, 12 and 24 hours:

	Introitus [ng/g]	Cervix [ng/g]
Before removal	6375	20047
	8 hours	
End of removal	3736	11583
[%]	58.60	57.77
	12 hours	
End of removal	2887	9022
[%]	45.29	45.00
	24 hours	
End of removal	1321	4123
[%]	20.72	20.57

Conclusion

Vaginal fluid concentrations of dapivirine at the introitus and cervix could be described adequately by a non-linear mixed effects model. Concentrations at the two locations could be described best when the release of dapivirine was described by a zero order together with a first order process. The model was used to predict vaginal concentrations after several application scenarios. When a ring is removed for 8, 12 or 24 hours after 28 days of wearing, vaginal fluid concentrations drop by 40, 55, and 80%, respectively. Successive replacements show virtually no accumulation.

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