Population PK/PD evaluation of the effect of dienogest on Hoogland Score in young healthy women

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Introduction

Dienogest (DNG) is a 19-nortestosterone derivative that exhibits selective binding to the progesterone receptor and displays neither agonist nor antagonist activity on glucocorticoid, mineralocorticoid or estrogen receptors and, importantly, neither androgenic activity. It is used for oral contraception and menopause management, as part of a combination treatment, and, as mono-preparation, for the treatment of endometriosis.

Objectives

The aim of our study was to develop a sequential PK/PD Model to characterize the concentration-response relationship with regard to Hoogland Score (HS), a common tool to assess ovarian function.

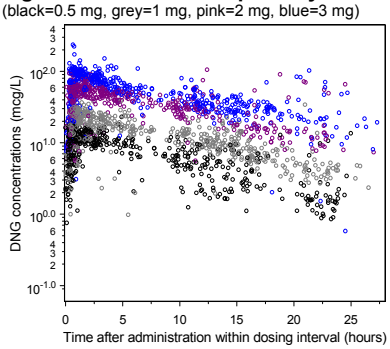
Methods

- Data was taken from a single-center, rando-mized, double-blinded, dose-controlled study in healthy female subjects investigating daily oral doses of 0.5 mg, 1 mg, 2 mg and 3 mg of DNG over up to 72 days [1].
- Steady-state AUC within dosing interval was selected as a predictor for the PD parameter HS, a categorical measure of the extent of follicular development which consists of 3 variables (follicle size, progesterone, and estradiol concentrations). HS data were collected before, and during treatment, and were grouped into three levels: HS 1 or 2: no or minimal ovarian activity, HS 3 or 4: residual ovarian activity, and HS 5 or 6: ovulation.
- Subsequent to the population PK analysis of DNG, an EMAX-like proportional odds model was implemented in NONMEM VI to construct a PK/PD description. Individual AUC values were calculated by AUC=D/(CL/F).
- Model selection was guided by decrease in objective function value (OFV, -2log likelihood) and by graphical exploration of goodness of fit plots for (i) probability – AUC trajectories, and (ii) deviations (DEV) between observations and predictions vs AUC, done in MATLAB R2009a.

Results

86 subjects provided a total of 1939 DNG serum concentrations and 172 HS values. The PK of DNG was best described by a linear two compartment model with first order absorption and elimination from the central compartment.

Figure 1 DNG scatter plots by dose
(black=0.5 mg, grey=1 mg, pink=2 mg, blue=3 mg)



Oral clearance (CL/F) and central volume of distribution were estimated with 3.47 L/h (RSE 2.9%) and 44.7 L (RSE 5.0%), respectively, and showed moderate interindividual variability of about 25%.

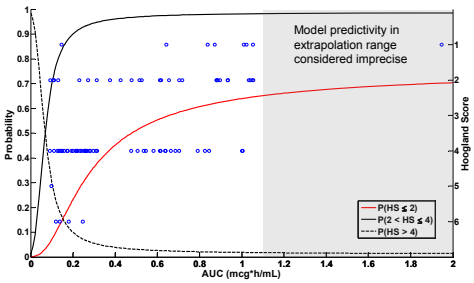
The logit, A_x, of probability of HS being at level 2, 4, 6 was modeled as an Emax-like function of DNG AUC as follows, assuming the same drug effect, EFF, for different scores:

A0 = B0 + EFF
A1 = B1 + EFF
where
B0 = ODDS1 (baseline logit for HS ≤ 2)
B1= B0 + ODDS2 (baseline logit for HS ≤ 4),
with EFF=EMAX*AUC/(AUC+AUC50),

Cumulative probabilities were calculated by
P0 = 1/(1 + EXP(-A0))
P1 = 1/(1 + EXP(-A1))
PR6 = 1 - P1
PR4 = P1 - P0
PR2 = P0

The predicted probabilities were in excess of 0.5 for a HS ≤ 2 and in excess of 0.9 for a HS ≤ 4, even for relatively moderate DNG exposures of 0.5 mcg*h/mL, for the 2 mg dose group.

Figure 2 Probability vs AUC plots



The performance of the model was evaluated by comparing the deviations between the model-predicted (PRED) and the observed (OBS) HS (Figure 5), where PRED is the estimated HS with maximum probability for given AUC. Overall, it shows a satisfying agreement between observed and simulated HS with a small trend of underprediction of the observed HS predominantly at higher AUCs. RSEs of parameters were moderate except for AUC50 (53%), likely due to the data distribution and the nonlinearity of the used model.

Table 1 Final Parameter estimates

Parameter	Final estimate	RSE [%]	LB of 95% CI	UB of 95% CI
EMAX	8.80	15.7	6.04	11.6
AUC50 [mcg*h/mL]	0.074	53.0	-0.004	0.153
ODDS1	-7.26	-15.9	-10.0	-5.20
ODDS2	3.40	15.8	2.33	4.47

RSE=relative standard error, CI=confidence interval, LB=lower bound, UB=upper bound

Sigmoidal Emax-like models with hill parameter n were explored. Figure 3 shows the probability of the HS being ≤ 2 versus the AUC for different n. For n = 2 and n = 2.5, a rise in the OFV was observed without improvement of the model fit. Estimation of n did not yield convergence and so the final model was chosen to be the original Emax model.

Figure 3 Effect of different n on probability curves

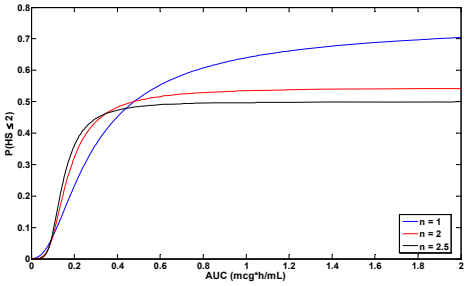
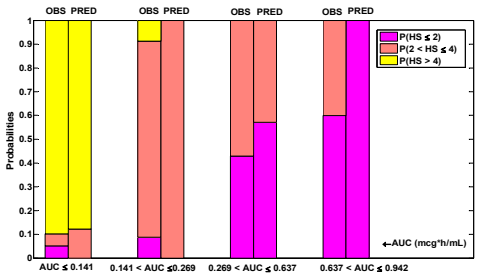
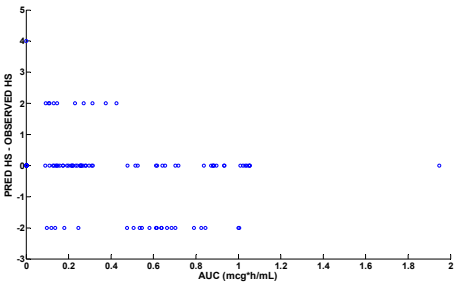


Figure 4 Histogram of obs. vs pred. HS grouped by median AUC per dose groups



For 81% of the data, the HS was correctly estimated. In 13% of the cases, the model overpredicted the efficacy, while for 6% the efficacy was underestimated. In 1 case (0.6%) a deviation of 4 was observed (see Figure 5). Orienting evaluations describing the logit of probability of HS as linear function of DNG AUC showed that the fit was significantly worse (+59.9 in OFV). In addition, the percentage of correctly estimated HS decreased to 75% and increased to 4% for cases with a deviation of 4.

Figure 5 Prediction error vs AUC



Future aspects of model optimization will include simulation-based model evaluation.

Conclusion

The PK/PD evaluation shows that DNG AUC is a good predictor for PD response in terms of Hoogland Score using a proportional odds model. The model may be further used for the prediction of ovulation inhibition based on DNG exposure.

Acknowledgements

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References

[1] Klipping C, Duijkers I, Faustmann T, Klein S, Schuett B. Pharmaco-dynamic study of four dosages of Dienogest. Fert&Ster 2010; 94(4) Suppl: 181