Impact of pharmacokinetic information reported as being below limit of quantification on the prediction of important response endpoints

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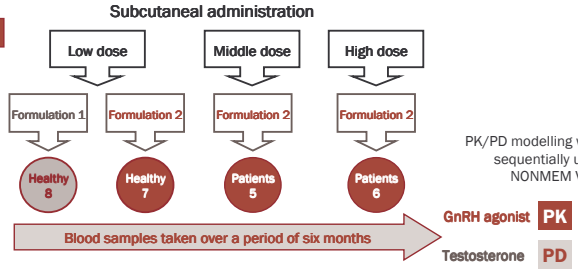
BACKGROUND AND OBJECTIVES

Pharmacokinetic (PK) and pharmacodynamic (PD) information are in occasions reported as being below limit of quantification (BQL). Most of the modelling experience with BQL information comes from PK analysis where the potential impact on the model parameters estimation has been discussed.

In the current analysis we provide an example in the context of hormone-related tumours, where BQL values in pharmacokinetics, without major effect on PK model estimates, have a clear impact on important pharmacodynamic endpoints.

METHODS



PK/PD modelling was done sequentially using NONMEM VI.

RESULTS

The percentage of BQL observations for the current analysis were 12.5% and 1.4% from the total of GnRH agonist (515) and TST (561) data, respectively. All of them were located 20 days after drug injection.

PK and PK/PD models were developed: A) excluding BQLs from the analysis or B) treating BQLs as censored observations according to method 3 in Beal 2001[1]. Pharmacokinetic and pharmacodynamic parameters of both analysis are given in Table I.

PK of GnRH agonist was best described using a one compartment disposition model and an absorption model characterized by a simultaneous zero- and first-order absorption which included a delay absorption compartment. The time profiles of TST were described using a variant of the pool-precursor model[2], where the GnRH agonist elicited a dual effect: (i) increasing the release of TST from the precursor compartment and (ii) blocking the synthesis of new precursors. (Figure 1).

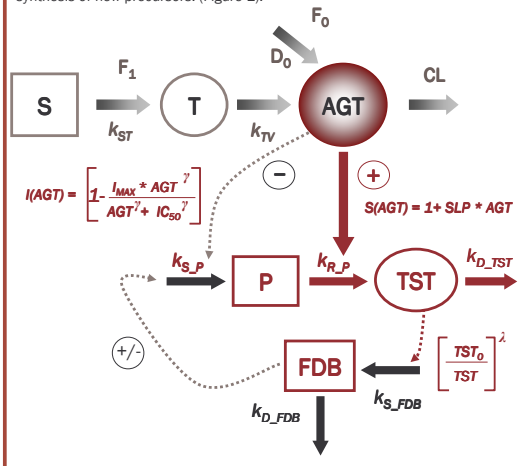


Figure 1. Pharmacokinetic - pharmacodynamic integrated model of the temporal course of testosterone.
S, subcutaneal compartment; T, transit depot compartment; AGT, concentration of agonist at central compartment, F_0 and F_1 fraction of dose absorbed following zero and first order process; D_0, duration of zero order absorption process; CL, Total clearance from central compartment; k_{ST} and k_{TV}, first order constants of absorption from subcutaneal depot to transit depot, and central compartment, respectively; *I(AGT)*, inhibition effect of AGT; I_{MAX}, the maximum inhibition of release rate; IC_{50}, concentration of agonist producing 50% of maximal inhibition; *S(AGT)*, stimulation effect of AGT; *SLP*, slope of the linear relationship between AGT and the release of testosterone; TST_0, concentration of testosterone at baseline; TST, concentration of testosterone in presence of AGT, γ, coefficient allowing sigmoidicity of the relationship between *I(AGT)* and AGT; λ, coefficient allowing physiologic values between TST_0 and TST; P, pool compartment; FDB, feedback compartment; k_{S_P} y k_{R_P} synthesis and release rate constants of pool, respectively; k_{D_TST}, degradation rate constant of testosterone; k_{S_FDB} and k_{D_FDB} synthesis and degradation rate constants of precursors at feed-back compartment; signs -,+ implies inhibition or stimulation effect.

Table I. Comparative pharmacokinetic and pharmacodynamic parameters of model excluding BQLs or including BQL as censored data observations.

	A) Excluding BQLs		B) BQLs as censored observations	
Parameters	Population mean	IIV	Population mean	IIV
Pharmacokinetics	**Estimate (RSE %)**	**CV (RSE %)**	**Estimate (RSE %)**	**CV (RSE %)**
F_1	0.20 (10.2)	0.21 (77)	0.09 (7.0)	0.34 (62.0)
V (L)	2180.0 (13.0)	0.35 (48.0)	2450.0 (16.4)	0.39 (43.0)
CL ($L.hr^{-1}$)	10.2 (9.7)	NE	11.6 (12.3)	NE
k_{ST} (hr^{-1})*	8.75 X 10^{-4} (20.0)	NE	1.11 X 10^{-3} (18.0)	NE
k_{TV} (hr^{-1})	8.75 X 10^{-4} (20.0)	NE	1.11 X 10^{-3} (18.0)	NE
D_0 (hr)	0.67 (6.2)	NE	0.67 (8.5)	NE
Residual error (µg/L)	0.54 (2.4)	NR	0.54 (2.4)	NR
Pharmacodynamics				
TST_0 ($µg.L^{-1}$)	4.42	0.88	4.52	0.26
k_{S_P} ($µg.h^{-1}.L^{-1}$)	0.041	-	0.042	-
k_{R_P} (h^{-1})	3.42 X 10^{-3}	0.74	3.18 X 10^{-3}	0.20
k_{S_FDB} ($µg.h^{-1}.L^{-1}$)	2.74 X 10^{-4}	-	3.99 X 10^{-3}	-
k_{D_FDB} (h^{-1})*	2.74 X 10^{-4}	-	3.99 X 10^{-3}	-
SLP ($µg^{-1}$ .L)	3.61	-	2.98	-
I_{MAX} (µmol/L)	7.46 X 10^{-4}	-	7.41 X 10^{-4}	-
IC_{50} (µmol/L)	1.90 X 10^{-5}	0.53	1.30X10^{-5}	0.66
γ	17.3	-	16.2	-
λ	0.331	-	0.131	-
Residual error (µg/L)	0.46	-	0.54	-

Bioavailability was considered as 1; $k_{ST} = k_{TV}$; $k_{S\_FDB} = k_{D\_FDB}$. The model parameters are explained in the text.

Behaviour of agonist pharmacokinetic and temporal course of testosterone are represented in figure 2 and 3 respectively. As we can see, principal differences are found in individual predictions of pharmacokinetics once BQLs observations were considered, meanwhile differences at testosterone predictions are not.

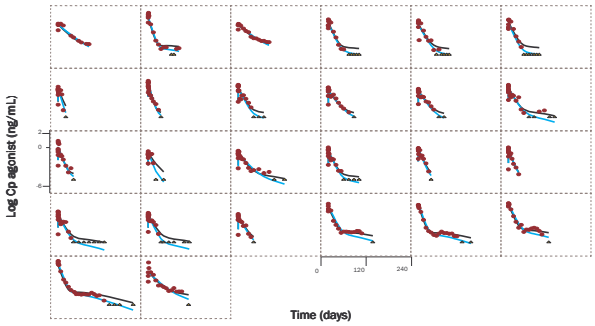


Figure 2. Individual agonist pharmacokinetics. ●Data observations above quantification limit; ▲Data observations below quantification limit (BQL); **black line**, predictions A); **blue line**, predictions B).

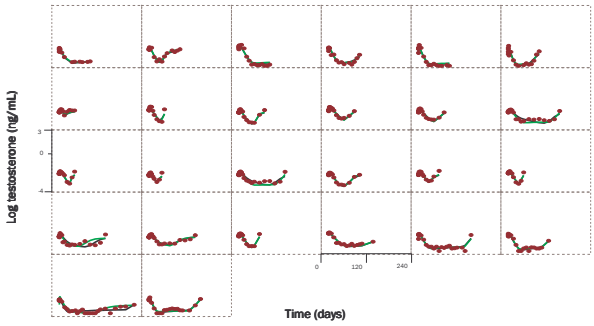


Figure 3. Individual time course of testosterone ●Data observations; **black line**, predictions A); **green line**, predictions B).

Regarding the most critical treatment endpoints, time of testosterone below 0.5 ng/mL (T_{cast}<0.5), model excluding BQLs of agonist (Figure 4, grey zone) predicted a median T_{cast}<0.5 of 35, 89, and 126 days for the low, middle, and high dose levels (grey bars on each panel).

When BQLs were treated as censored observations (Figure 4, green zone) the corresponding values of T_{cast}<0.5 were 49, 78, and 92 days respectively, (green bars) and dispersion of data diminished substantially.

PD models proposed by other authors[3] were explored by incorporation of our PK model (Figure 4, blue lines). Graphics shown mainly, differences between estimation of T_{cast} (blue bars) at middle and high doses were HPG axis model estimate nearest periods of time (65 and 58 days) even at different doses.

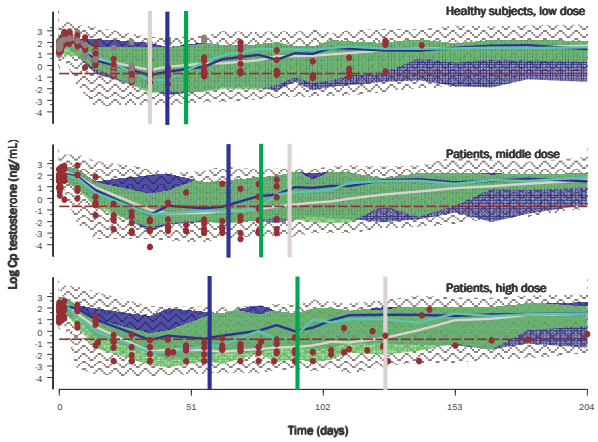


Figure 4. Internal validation of the model. Grey zone: PK/PD model excluding BQLs; **green zone:** PK/PD model using BQLs as censored observations; **blue zone:** PK and PD model from Tornoe and cols.[3] using BQLs as censored observations; **grey** and **red** symbols represent testosterone observations in plasma of both formulations (1 and 2 respectively); solid bold lines represent 50th percentile obtained from 1000 simulated profiles at each condition. Segmented red line represents testosterone level at 0.5 ng/mL. Vertical bars correspond to the time at which testosterone levels are above castration time (T_{cast} > 0.5 ng/mL).

CONCLUSIONS

The current analysis shows the importance of considering BQL observations in pharmacokinetics, even in cases where the impact on populations PK parameters is marginal. This methodology is especially indicated in those cases where there is a strong correlation between plasma drug concentrations and pharmacodynamic endpoints.

REFERENCES

[1] Beal SL. J Pharm Pharmacodyn; 28: 481-504 (2001).
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