Pharmacokinetic characterization of naphtalophos in lambs by modelling blood acetylcholinesterase activity, a K-PD model

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BACKGROUND

Naphthalophos (NAF) is a widely used organophosphate for the control of sheep gastrointestinal nematode infection given its broad spectrum and its efficacy against anthelmintic-resistant worms.

Pharmacokinetics of oral NAF suspensions in sheep, which are essential to define withholding periods (WHP) and compare available formulations, have been scarcely studied. NAF blood concentrations are difficult to measure given its rapid elimination through blood esterases, however the reported meat WHP of 7 days for Rametin® (Bayer, original formulation) indicates that a significant distribution into tissue is taking place [1].

The aim of this work was to develop a K-PD model [2] describing acetylcholinesterase (AChE) activity after NAF oral administration in order to:

- Estimate absorption rate and residence time.
- Evaluate the effect of food intake and dose on NAF absorption.
- Further comparison of NAF PK between formulations marketed in Uruguay.

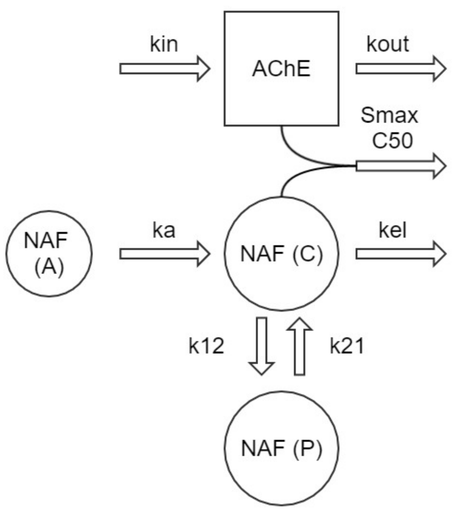
METHODS

One hundred (100) Corriedale lambs were involved in the current experiment under regular field conditions (Uruguay). The animals were randomly allocated into five groups (n=20 each): an untreated control group and four groups treated with a single NAF oral dose of 10, 30, 50 and 70 mg/kg of Tritom NF ® (NAF 15%, Compañía Cibeles S.A.). Twenty-five animals (5 of each group) received the dose in fasting conditions. Five blood samples per animal were obtained over the 28 days post-dosing period. Samples were immediately stored and kept at -18°C until analysis. AChE activity in red blood cells was determined using a modified Ellman assay. Population analysis was done in NONMEM 7.3 [3]. Pirana, PsN, Xpose and PKPDsim were used in model development and graphic outputs. Study groups:

CONTROL GROUP Fed n=15 Fasting n=5	NAF 10 mg/kg Fed n=15 Fasting n=5	NAF 30 mg/kg Fed n=15 Fasting n=5	NAF 50 mg/kg Fed n=15 Fasting n=5	NAF 70 mg/kg Fed n=15 Fasting n=5

RESULTS

Figure 1. Structural model



$$\frac{dAChE}{dt} = k_{in} - k_{out} * AChE * (1 + NAF_C * \frac{S_{MAX}}{C_{50} + NAF_C})$$

$$\frac{dNAF_A}{dt} = -k_a * NAF_A$$

$$\frac{dNAF_C}{dt} = k_a * NAF_A - k_{out} * AChE * \left(1 + NAF_C * \frac{S_{MAX}}{C_{50} + NAF_C}\right) - k_{el} * NAF_C + k_{21} * NAF_P - k_{12} * NAF_C$$

$$\frac{dNAF_P}{dt} = k_{12} * NAF_C - k_{21} * NAF_P$$

$$AChE_i(t=0) = BL * e^{\eta_i}$$

Parameter	Units	Estimate (%RSD)	95% CI	Comments
BL	µmol/mL/min	1.62 (1.69)	1.56 - 1.67	AChE activity baseline. BL = kin/kout
Kout	h^{-1}	0.0129 (10.2)	0.0109 - 0.0165	first-order constant rate for AChE elimination
S_{MAX}	---	19.3 (15.6)	15.1 - 25.9	maximum kout stimulation by NAF
C50	mg/kg	0.724 (12.2)	0.558 - 0.922	NAF (mg/kg) producing 50% of S_{MAX}
ka	h^{-1}	1.06 (18.3)	0.839 - 1.72	first-order constant rate for NAF absorption
kel	h^{-1}	5.54 (15.1)	4.47 - 7.70	first-order constant rate for NAF metabolism by non-AChE processes
k12	h^{-1}	1.41 (15.9)	1.04 - 1.80	first-order constant rate for NAF distribution into peripheral compartment
k21	h^{-1}	0.0280 (14.5)	0.0192 - 0.0346	first-order constant rate for NAF distribution into central compartment
Res	---	18.6% (5.42)	16.7 - 20.6	proportional residual error. ε-shrinkage: 9%
IIV BL	---	10.8% (24.2)	7.94 - 13.4	η-shrinkage: 21%
IIV ka	---	135% (47.0)	40.4 - 300	η-shrinkage: 58%

Table 1. Parameter estimates from bootstrap (n=1000)

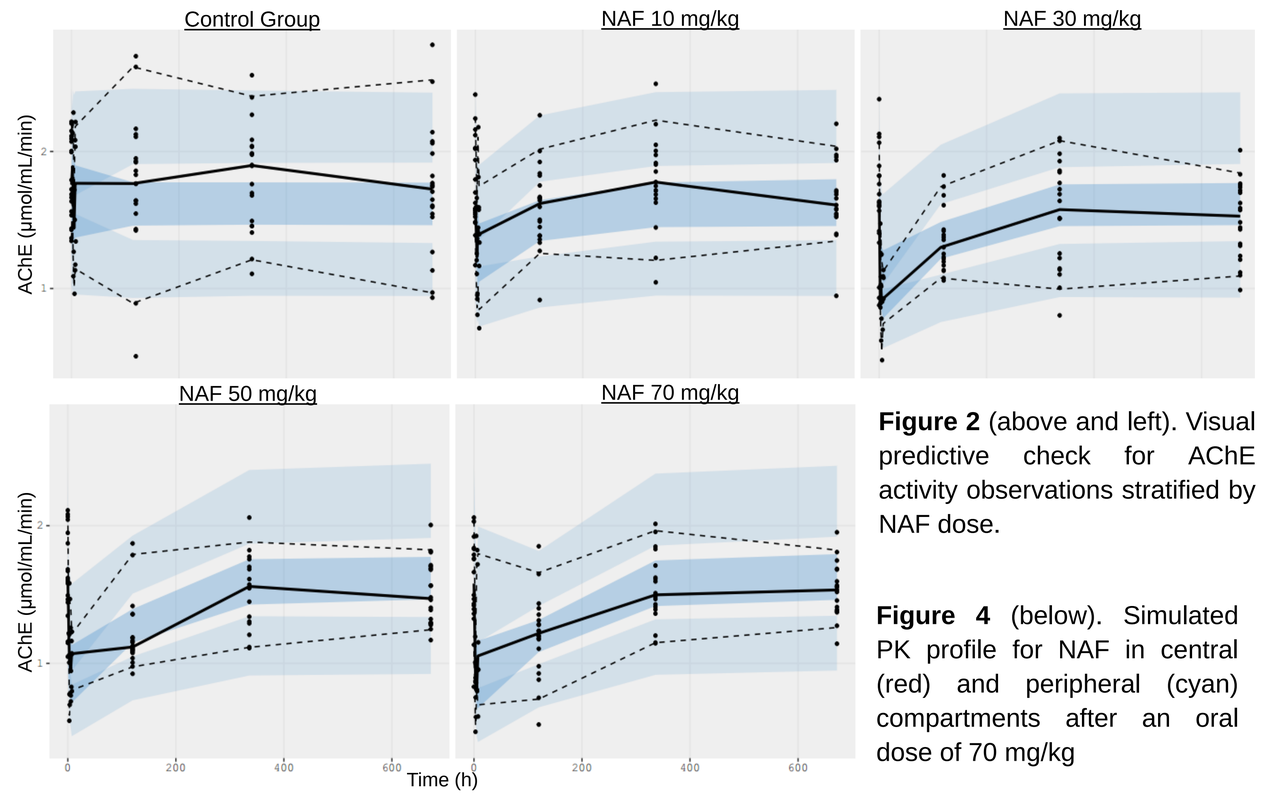


Figure 2 (above and left). Visual predictive check for AChE activity observations stratified by NAF dose.

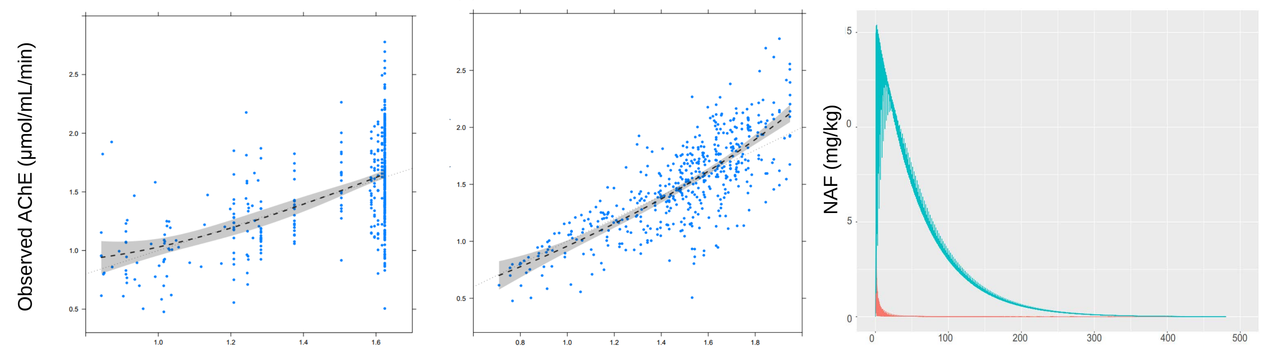


Figure 4 (below). Simulated PK profile for NAF in central (red) and peripheral (cyan) compartments after an oral dose of 70 mg/kg

Figure 3 (above). Observations vs population and individual predictions for AChE activity in blood.

- The model described AChE typical tendency and captured interindividual variability.
- Inclusion of fasting condition and NAF dose as covariates on ka produced no significant improvements in data fit.
- Estimated kout is in agreement with platelet lifespan reported for sheep blood of 80 days.
- Considering a maximum residue level of 0.01 mg/kg for peripheral compartment, a theoretical withholding period of 14 days was estimated.

CONCLUSION

A pharmacokinetic profile for NAF was obtained, allowing estimation and population analysis of NAF input and disposition kinetics. This model could be further used to assess systemic NAF exposure produced after administration of the different formulations marketed in Uruguay.

REFERENCES

1. RAMETIN® package insert. BAYER, 2003.
2. Jacqmin P, Snoeck E, van Schaick EA, Gieschke R, Pillai P, Steimer JL, Girard P. Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. J Pharmacokinet Pharmacodyn 2007;34(1): 57-85.
3. Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J. NONMEM User's Guides 1989-2009; Icon Development Solutions, Ellicott City, MD, USA, 2009.