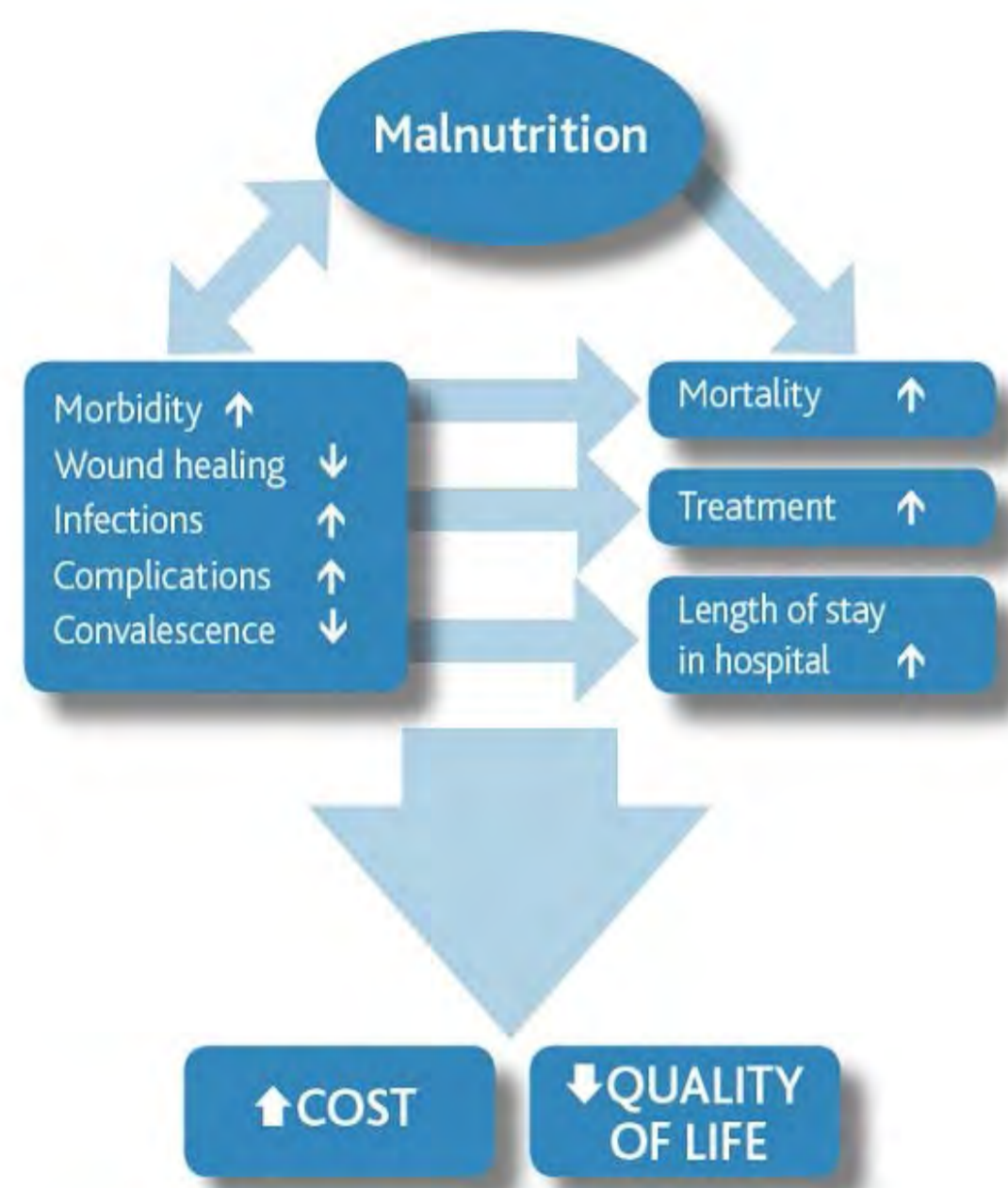


A Mechanistic Population Pharmacokinetic Model For Taurine In Well And Undernourished Rats

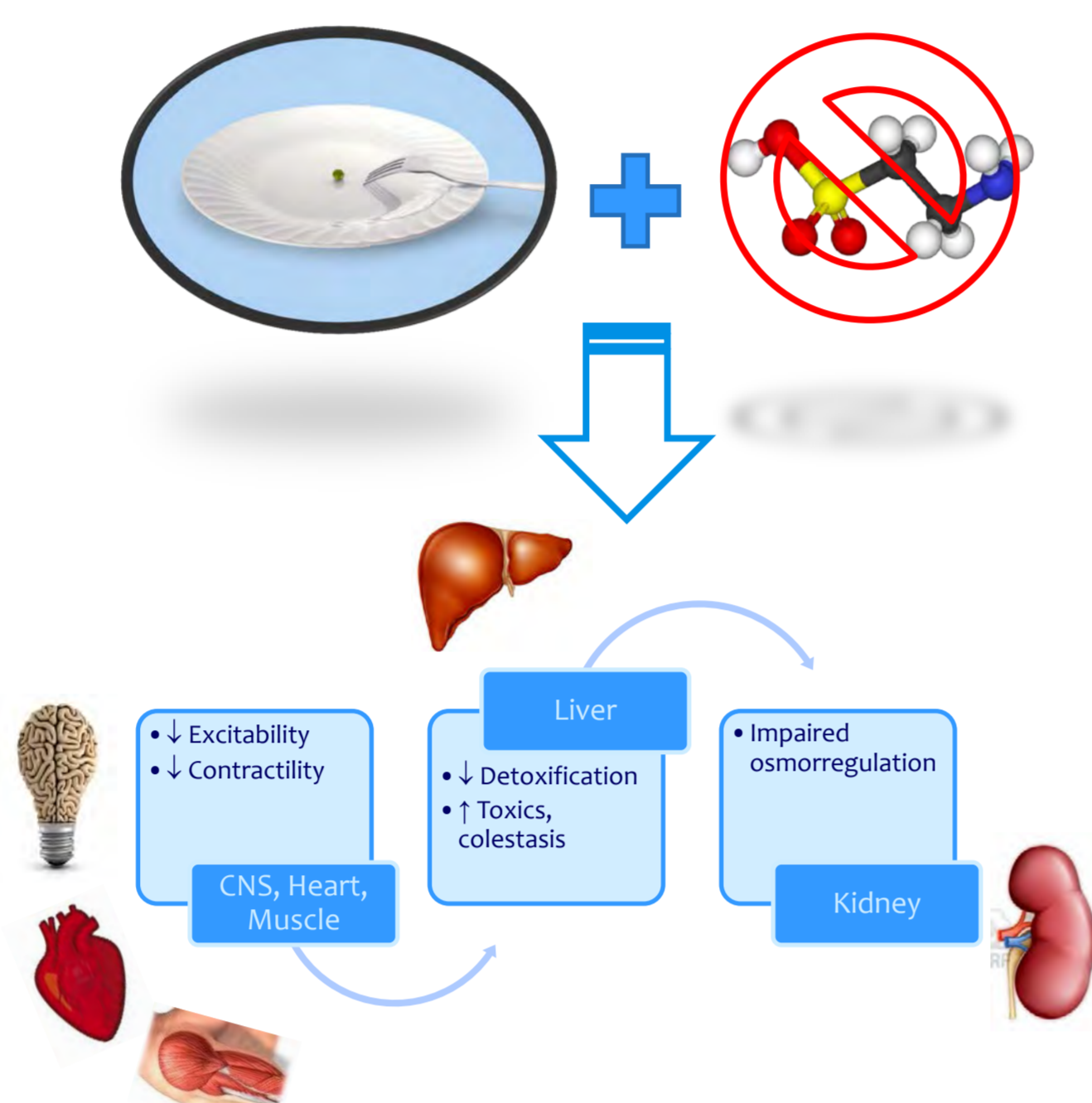
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INTRODUCTION



Protein-energy undernutrition (PEU) can seriously compromise the outcomes of other pathologies since pathophysiological derangements in patients with PEU have a profound impact on absorption, protein binding, metabolism and elimination of drugs¹⁻³

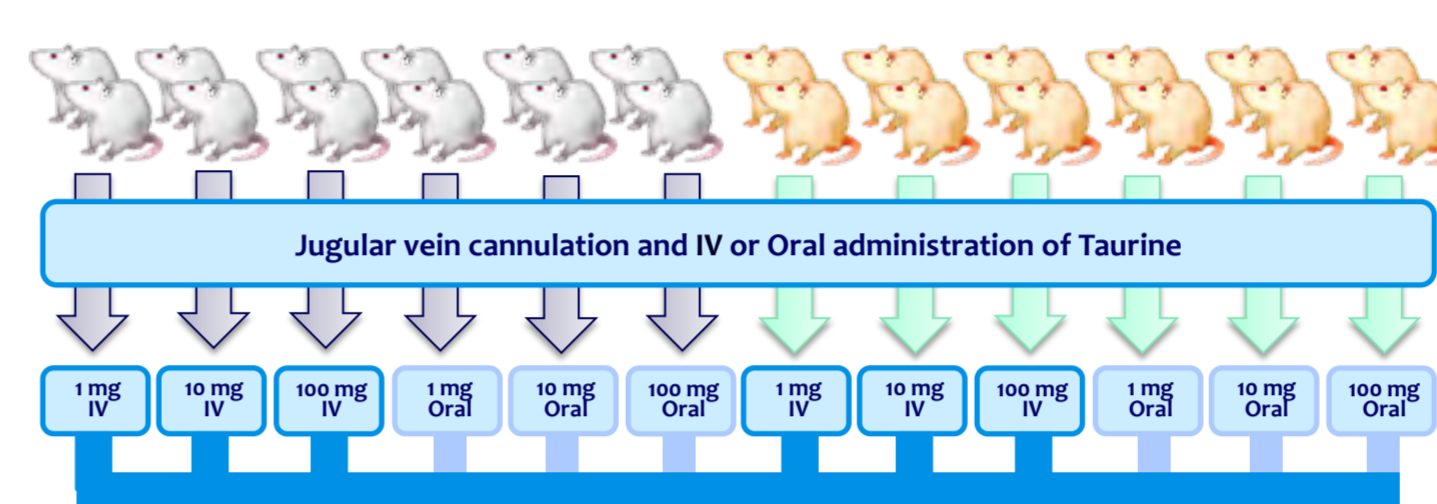


Taurine is an endogenous conditionally essential amino acid involved in numerous biological processes and its needs increase in response to pathological conditions⁴.

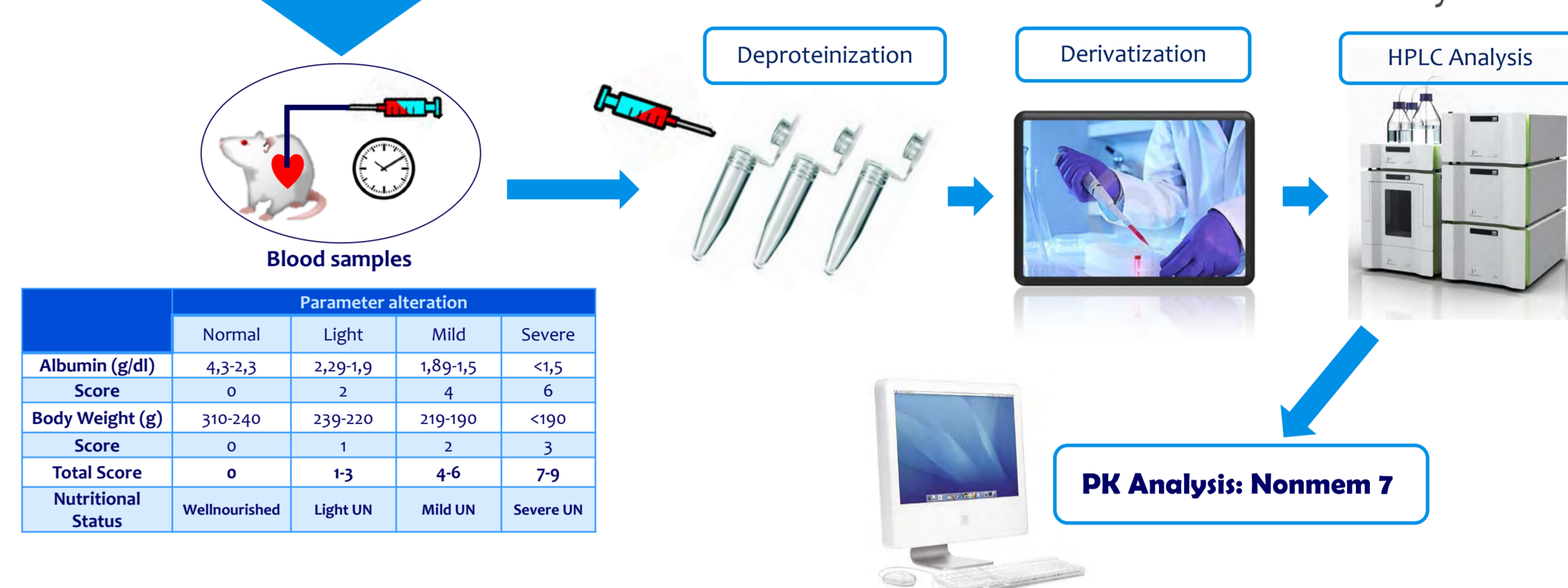
The aim of this study was to perform a PK modelling to describe the behavior of taurine in well-nourished rats and analyze the influence of PEU on the PK parameters of taurine in undernourished rats.

MATERIAL AND METHODS

Wistar rats were randomly distributed in two groups -WN (well-nourished) and UN (undernourished) - and were fed with different diets for 23-26 days⁵. During this time, weight was recorded daily and serum albumin was registered weekly.



After this time, nutritional status was assessed and taurine was administered intravenously (IV) or orally (PO) to WN and UN rats at different doses: 1, 10, and 100 mg (N=68). Plasma samples were collected for taurine and were analyzed by HPLC



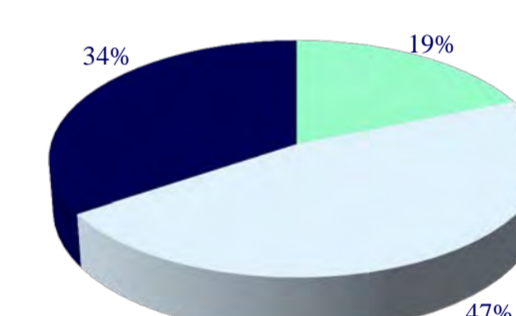
Parameter	Nutritional alteration			
	Normal	Light	Mild	Severe
Albumin (g/dl)	4,3-2,3	2,29-1,9	1,89-1,5	<1,5
Score	0	2	4	6
Body Weight (g)	310-240	239-220	219-190	<190
Score	0	1-3	2	3
Total Score	0	1-3	4-6	7-9
Nutritional Status	Wellnourished	Light UN	Mild UN	Severe UN

Population pharmacokinetic modelling was performed using nonlinear mixed effects software (NONMEM 7.0) with FO estimation. Several distribution and absorption models were explored in combination with dose and/or time covariate effects. Covariates such as nutritional status, serum albumin, body weight and score of undernutrition were used.

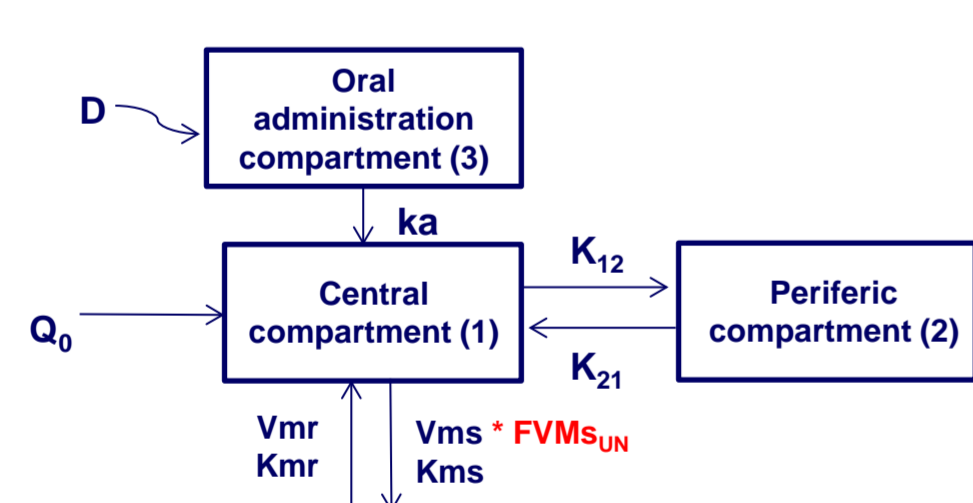
RESULTS AND DISCUSSION

UNDERNUTRITION STATUS

At the end of the adaptation period, all animals in PEU group were classified as light (19%, green) mild (47%, light blue) or severe (34%, blue) undernourished depending on weight and albumin levels. 100% of WN animals were classified as well-nourished.

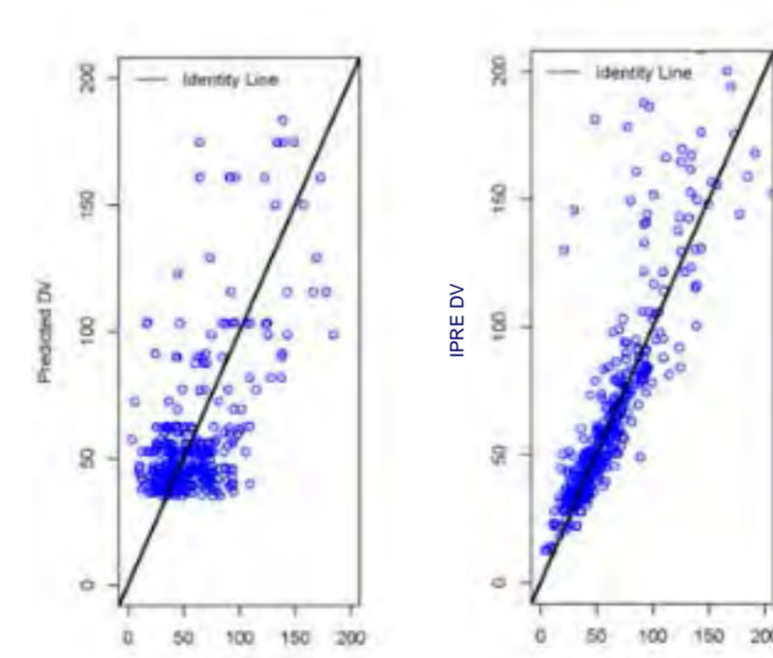


MODEL

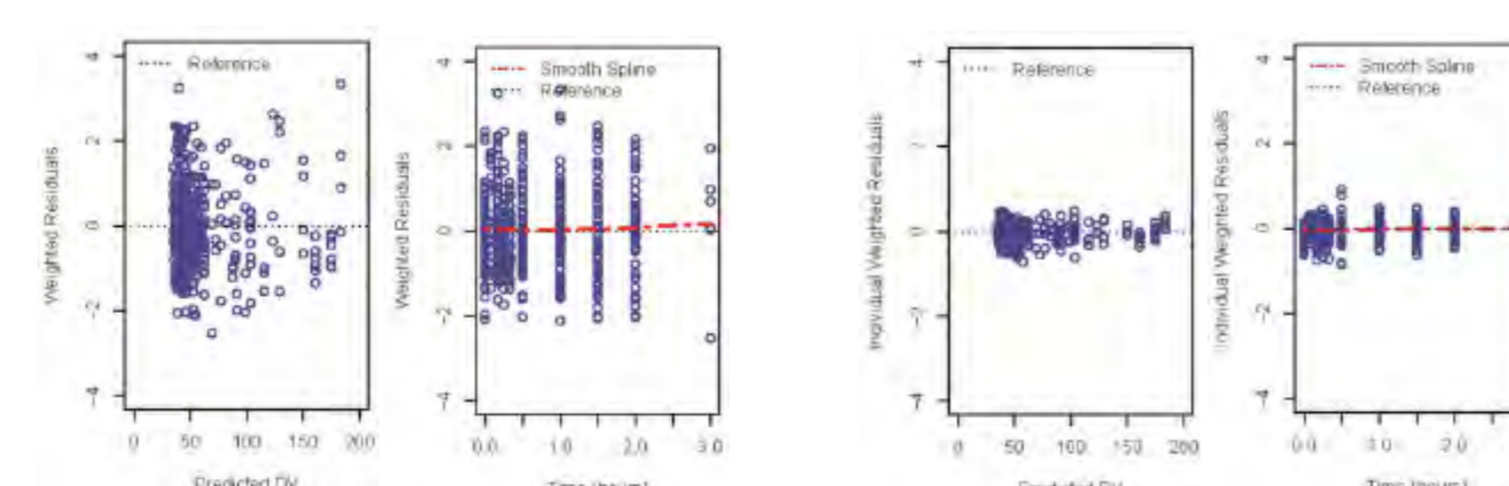


A two-compartment population pharmacokinetic model with zero order endogenous formation, passive absorption, first order kinetics distribution and nonlinear elimination with parallel Michaelis-Menten excretion and reabsorption processes best described taurine pharmacokinetics. When models were scaled for malnutrition, undernutrition acted as covariate reducing the Vmax of the active elimination process. Goodness of fit plots (GOF) showed reasonable good results.

GOODNESS OF FIT PLOTS



Correlation between experimental taurine concentrations (Observed DV) vs population predicted concentrations (Predicted DV, left) and individual predicted concentrations (IPRE DV, right)



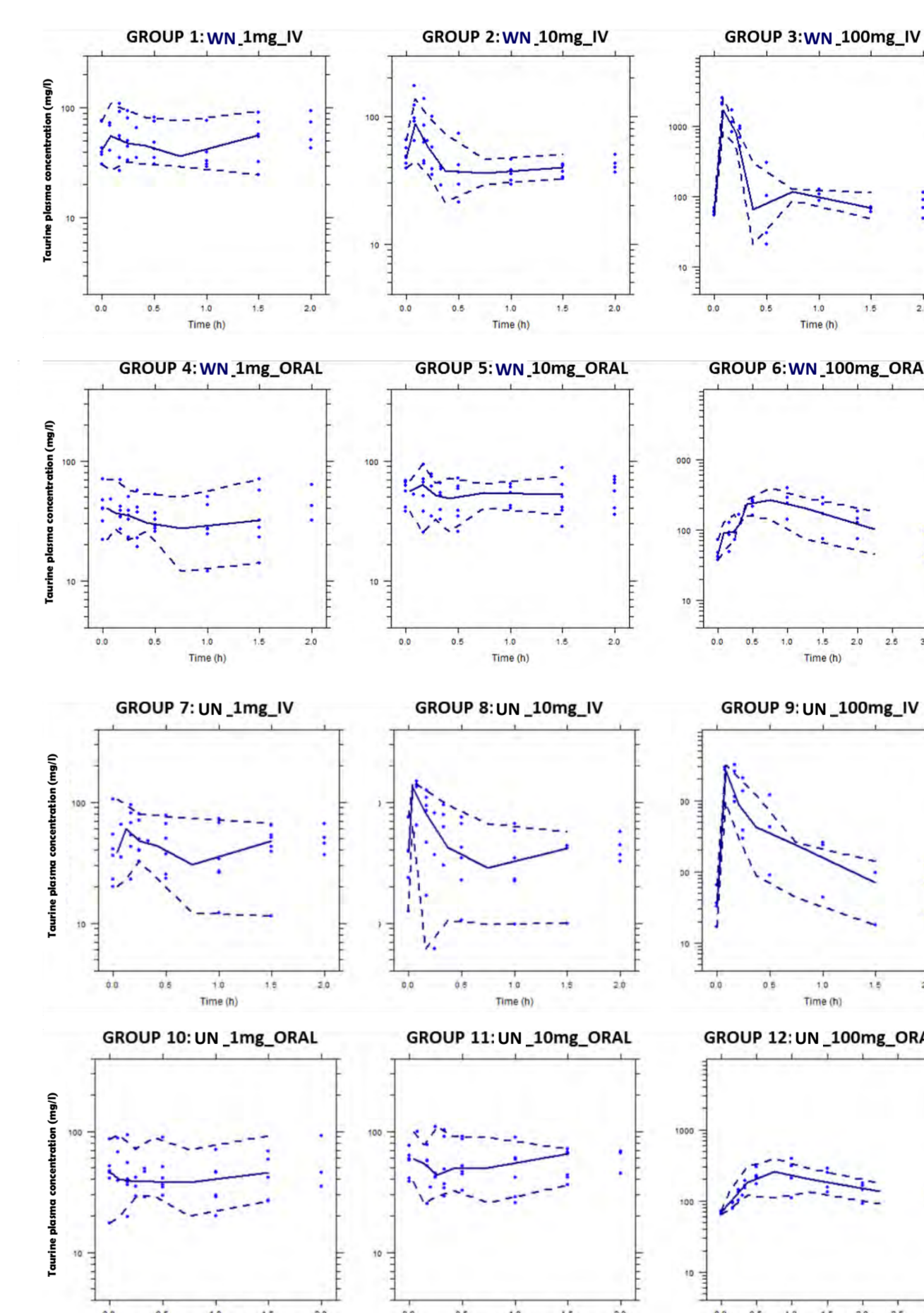
Weighted residuals (left) and Individual weighted residuals (right) vs predicted plasma concentrations (mg/l) or time of blood sampling (hours)

INTERNAL VALIDATION: BOOTSTRAP

PPK Parameter	Original Data Base		Bootstrap Replicates		
	Estimation	CV%	Mean	CV%	IC 95%
Estructural Pharmacokinetic Model					
Q ₀	13,7	36,0	14,4	29,0	9,21-23,8
V _c	0,0416	17,5	0,0462	14,9	0,036-0,061
K ₁₂	2,61	44,8	2,32	27,2	1,15-3,47
K ₂₁	0,73	48,1	0,893	45,5	0,314-1,74
V _{ms}	192,0	56,3	331	89,5	78,1-1041
K _{ms}	399	110	780	121	75,8-3391
V _{mr}	16,9	457	89,1	228	0,268-786
K _{mr}	96,1	190	266	509	1,91-1808
FV _{ms}	0,906	15,1	0,950	6,51	0,823-1,06
K _a	1,19	18,2	0,969	23,4	0,575-1,45
Interindividual Variability					
VII _{Q0}	25,7	104	20,5	51,1	0,257-35,2
VII _{Vc}	50,6	52,7	66,4	28,7	31,9-98,5
VII _{K12}	120,4	38,7	101	37,1	55,3-156
VII _{K21}	93,4	293	109	118	0,934-326
VII _{Vms}	17,1	285	11,7	86,1	0,171-30,7
VII _{Ka}	69,6	42,3	29,7	108	0,600-82,1
Residual Variability					
σ	22,4	10,0	21,5	6,50	18,8-24,2

Results of the Bootstrap resampling technic

INTERNAL VALIDATION: VPC



VPC of the selected model. Dots experimental points. Lines are referred to percentils 5, 50 and 95 from simulated data. NN; wellnourished animals, UN: Undernourished animals

CONCLUSIONS

- Data analysis showed linear absorption and distribution, and non-linear elimination processes for taurine. Elimination of taurine was reduced a 10% in undernourished animals, suggesting that the reabsorption process via the secretion transporter was modified in this group.
- PK modelling provides a useful tool to describe the levels of taurine and offers a robust method to understand the changes in PK occurred in undernourishment.

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