Exposure-Response Modeling and Simulation to Support Human Dosing for Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine) or BAT™

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ABSTRACT

Background: An exposure-response modeling and simulation was performed to support Cangene's approved human dosing recommendations for BAT™, Botulism Antitoxin Heptavalent (A,B,C,D,E,F,G) - (Equine).

Methods: A compartmental model was constructed to assess the pharmacokinetics (PK) of BAT in humans, guinea pigs and rhesus macaques. A traditional allometric power model was used to scale compartmental PK parameters in humans according to the corresponding body weight of each species. This relationship was used to simulate exposure to BAT in any species and according to any dosing scenarios. Subsequently, an exposure-response model was constructed to provide a mechanistic understanding of the relationship between exposure to BAT and response to BoNT intoxication (survival) based on the available post-exposure prophylaxis study information (guinea pig and rhesus macaque). Exposure to BAT was simulated using the PK model and survival probability in humans was predicted based on the above exposure-response model.

Results: BAT exposure (AUC) in humans was compared to a minimum efficacious exposure (MEE) to identify the margin of efficacy (MOE = $AUC_{Human\ Dose}$ /AUC_{MEE}). The MOE ratio provides an estimate of the "safety" margin for the product. A summary of the MOE for each BoNT serotype and the probability of survival in humans are presented in the table below.

Serotype	Label Claim (U/vial)	AUC (U*hr/mL)	MEE (U*hr/mL)	MOE	Survival Probability
A	> 4,500	9.07	0.249	>36.4	99.9
B	> 3,300	8.14	0.409	>19.9	95.6
C	> 3,000	10.0	0.936	>10.7	97.5
D	> 600	1.71	1.601	>1.07	93.1
E	> 5,100	2.50	1.064	>2.35	99.0
F	> 3,000	8.50	0.166	>51.2	99.5
G	> 600	2.37	0.102	>23.2	97.4

Conclusions: Based on the exposure-response models, the MOE for all antitoxin serotypes were above 1 and the predicted probability of survival in humans following exposure to all serotypes of BoNT was more than 93.1% following administration of the one vial of BAT.

INTRODUCTION

BAT is an antitoxin consisting primarily of F(ab')2, and Fab' plus F(ab')2 related immune globulin fragments derived from horses immunized with *Clostridium botulinum* (*C. botulinum*) toxoids and toxins. Cangene Corporation has developed BAT to specifically neutralize toxins produced by *C. botulinum*. BAT is a heptavalent product intended for the treatment of symptoms following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F or G.

OBJECTIVE

The objective of the current analysis is to present pharmacokinetic (PK) and pharmacodynamic (PD) modeling results using available data related to guinea pigs, non-human primates (NHP) and humans in order to support the human dosing regimen of BAT.

METHODOLOGY

Initially, a compartmental PK model was constructed to assess the PK of BAT for each species, based on data collected from the Cangene Corporation pre-clinical/clinical studies. A traditional allometric power model was used to scale compartmental PK parameters in humans according to the corresponding body weight of each species[1]. This relationship can be used to simulate body burden of BAT in any species and any dosing scenario.

Subsequently, an exposure-response model was constructed in order to provide a mechanistic understanding of the relationship between body burdens of BAT and response (survival and clinical signs) to BoNT. Exposure to BAT was simulated using the PK model and response was taken from available post-exposure prophylaxis studies. This model was leveraged to support the optimal clinical dose levels of BAT. These mechanistic models were used to explore the relationship between BAT exposure as predicted by the population PK model (area under the concentration curve (AUC)), ~~and~~ the probability of survival and the occurrence of relevant moderate clinical signs observed during the pre-clinical development of BAT.

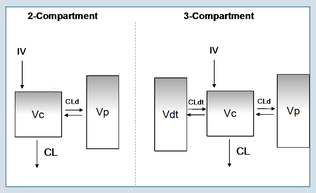
RESULTS

PHARMACOKINETICS (PK) IN GUINEA PIGS, NHPS AND HUMANS

Table 1: Summary of PK Data Used in the PK Model

Species	# of Single Dose PK Datasets	# of Serotypes	BAT Alone	BoNT Challenge
Guinea Pig	1	7	Yes	No
Non-human Primate	2	1 (A)	Yes	Yes
Human	1	7	Yes	No

Figure 1: Conceptual Structural PK Models for BAT



Vc is the central volume of distribution of BAT, CL is the clearance of BAT, Vp is the peripheral volume of distribution of BAT, CLd is the distribution clearance of BAT, and CLdt is the distribution CL to the deep tissue compartment which has a volume of distribution corresponding to Vdt.

Table 2: PK Model Parameters (Normalized by Body Weight)

Parameter	PK Parameters of BAT (Geometric Mean)						
	Serotype A	Serotype B	Serotype C	Serotype D	Serotype E	Serotype F	Serotype G
CL (mL/h/kg)	14.75	10.82	8.08	4.44	7.72	12.25	10.01
CLd (mL/h/kg)	2.70	7.24	16.17	5.29	0.88	43.40	2.84
CLdt (mL/h/kg)	8.15	136.03	4.56	2.63	NA	2.53	40.48
Vc (mL/kg)	31.88	21.32	56.45	0.66	0.25	32.44	20.56
Vp (mL/kg)	21.17	145.29	25.44	14.93	4.19	44.23	67.04
Vdt (mL/kg)	23.38	34.39	1227.12	5.44	NA	40.94	28.03
Proportional Error (%)	24%	34%	45%	30%	38%	35%	35%

NA = Not Applicable, Serotype E concentrations were best explained by a 2-compartment model.

We can use this PK model to determine the exposure in animal efficacy studies where no PK samples were collected or to simulate the human exposure for any proposed human dose level.

EXPOSURE-RESPONSE (PD) IN GUINEA PIGS AND NHPS

Table 3: Summary of PD Data Used in the PD Model

Animal	BoNT Serotype	Survived[a]
NHP	A	20/20 (100%)
	B	ND
	C	ND
	D	ND
	E	ND
	F	ND
	G	ND
Guinea Pigs	A	70/80 (87.5%)
	B	73/80 (91.3%)
	C	70/80 (87.5%)
	D	42/80 (52.5%)
	E	56/78 (71.8%)
	F	75/80 (93.8%)
	G	76/80 (95.0%)

[a] Values represent Yes / Total (Percentage)
ND = Not Determined

LOGISTIC REGRESSION

Figure 2: Logistic Regression of Body Burden of BAT vs. Survival (Serotype A)

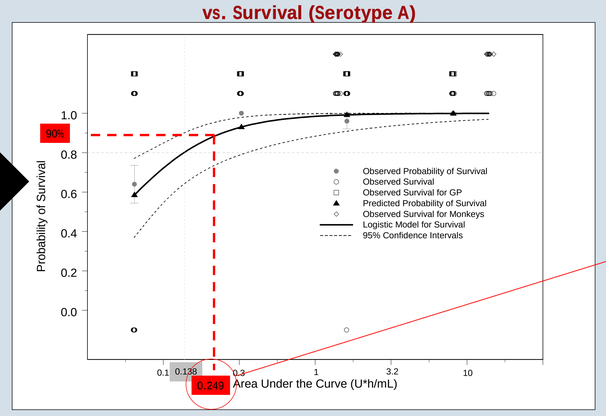


Table 4: Predicted Probability of Survival as a Function of BAT Exposure (Serotype A)

Survival Probability	BAT AUC (U*h/mL)
58.3%	0.064
70.3%	0.094
80.1%	0.137
90.2%	0.249
95.1%	0.429
99.0%	1.415

BAT AUC of 0.249 U.h/mL represents the threshold over which human exposure must be in order to be protective according to the animal models (>90% protection). We term this "minimum efficacious exposure " (MEE).

SIMULATION OF ACHIEVED PROTECTION IN HUMANS AT THE PROPOSED HUMAN DOSE

BAT exposure (AUC) in humans following a proposed dose of 1 vial was compared to the MEE to identify the margin of efficacy (MOE = $AUC_{Human\ Dose}$ /AUC_{MEE}). The MOE ratio provides an estimate of the "safety" margin for the product[2,3].

Table 5: Margin of Efficacy for 90% Survival of BAT Serotype A-G

Serotype	Label Claim (U/vial)	AUC (U*hr/mL)	MEE (U*hr/mL)	MOE	Survival Probability
A	> 4,500	9.07	0.249	>36.4	99.9
B	> 3,300	8.14	0.409	>19.9	95.6
C	> 3,000	10.0	0.936	>10.7	97.5
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DISCUSSION

Exposure levels of BAT predicted with the PK/PD model for the survival endpoint across all serotypes and the proposed clinical dose (1 vial) was deemed efficacious against all serotypes of BoNT in terms of probability of survival. Overall, based on the data currently available, probabilities of survival following exposure to serotypes A, B, C, D, E, F, and G of BoNT were >93% following a dosing of 1x BAT. The MOE of BAT to serotypes A, B, C, D, E, F, and G of BoNT were >1. A high MOE gives the flexibility to decrease the administered dose, in times of product shortages, and still be greater than the efficacy benchmark set in pre-clinical animals. Similarly, this margin can help assess efficavy for any potential decrease in BAT body burden due to increases in BoNT dose and any possible interaction between the two internal doses of BAT and BoNT.

The greater toxicity of BoNT serotypes D and E was reflected in the MOE for (~1.1 and ~2.4, respectively). For these, a 25% decrease in BAT dose or exposure (due to variability) would possibly result in an unacceptable loss of efficacy as protection of from these serotypes would possibly fall below 90%.

The relationship between the body burden of BAT and the four moderate clinical signs (change in breathing rate patterns, increased salivation, increased lacrimation, presence of weak limbs) following BoNT administration from the guinea pig efficacy study was also evaluated using logistic regression models and provided an accurate level of protection.

These mechanistic models were used to explore the relationship between BAT exposure measures predicted by the population PK model area under the concentration curve (AUC)) and the probability of survival and the occurrence of relevant moderate clinical signs observed during the pre-clinical development of BAT. The predicted probability of survival in humans for all serotypes of BoNT was more than 95.9% following IV administration of 1x BAT. Furthermore, in humans a single dose of BAT is expected to result in significant protection and reduced clinical signs of intoxication against all BoNT serotypes. Since BAT is expected to be in excess of BoNT, there is currently no experimental evidence suggesting that increasing doses of BoNT would alter level of protection.

REFERENCES AND ACKNOWLEDGMENT

1. Gabrielsson, J., Weiner, D. 2006. Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications (4th Edition). Swedish Pharmaceutical Press, Stockholm, Sweden.
2. Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc JC, Renwick AG, Setzer W, Schlatter J, Smith B, Slob W, Williams G, Wildemann T. 2010. Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food Chem Toxicol. 48:S2-24.
3. Dybing E, O'Brien J, Renwick AG, Sanner T. 2008. Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Toxicol Lett. 180:110-7.

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