



Rational dosing of caffeine using target concentration intervention to improve treatment of apnea of prematurity

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Objectives

1. To link the time course of caffeine in premature neonates with a hazard model for the occurrence of AOP.

2. To identify a target concentration for prevention of AOP using caffeine.

Background

Apnea of prematurity (AOP) is defined as an attack of apnea for at least 20 seconds, with bradycardia and cyanosis. It is a common phenomenon in the neonatal intensive care unit. Caffeine is used to suppress or to prevent AOP attacks.

Methods

Caffeine concentrations were measured prospectively in a study of its pharmacokinetics (PK) in premature neonates with AOP (Yang 2019). The PK was described with a mixed effect one compartment first order elimination model. The baseline hazard was described by a Gompertz distribution. The pharmacodynamics (PD) of caffeine were modelled using a sigmoid Emax model reducing the hazard of an AOP attack. PD covariates included adenosine receptor (AR) genotype and various methods of spontaneous breathing ventilation support (LFNC, HFNC, CPAP, BIPAP, BNCPPAP) or mechanical ventilation (CMV, HOV). The hazard was set to 0 during mechanical ventilation (HAZVENT). The pharmacodynamic (PD) and hazard model was developed using NONMEM 7.41. Visual predictive checks (VPC) were performed for model evaluation.

Results

Caffeine concentrations (1004 measurements) with fixed protocol dosing in 222 premature neonates had a wide distribution (median 8.7 mg/L, 90% within 2.9 and 18.1 mg/L after 2 days of treatment). Both fixed (size and post-menstrual age) and random effects on between subject variability in clearance were important. Between occasion variability in clearance was small.

There were 822 AOP events. The bootstrap hazard and PD parameter estimates are shown in Table 1. AR genotype was not associated with caffeine PD. A Kaplan-Meier VPC of AOP events shows good predictive performance (Figure 1).

The PD parameters were used to simulate the link between caffeine concentration and reduction of AOP hazard (Figure 2). The C50 suggests that a target concentration of 5 mg/L would achieve close to maximum achievable benefit and this was chosen as the target concentration.

A Bayesian dose forecasting procedure was developed using NextDose which clinicians can use to calculate initial doses and then use measured caffeine concentrations to further individualize treatment to achieve the target concentration.

Funding

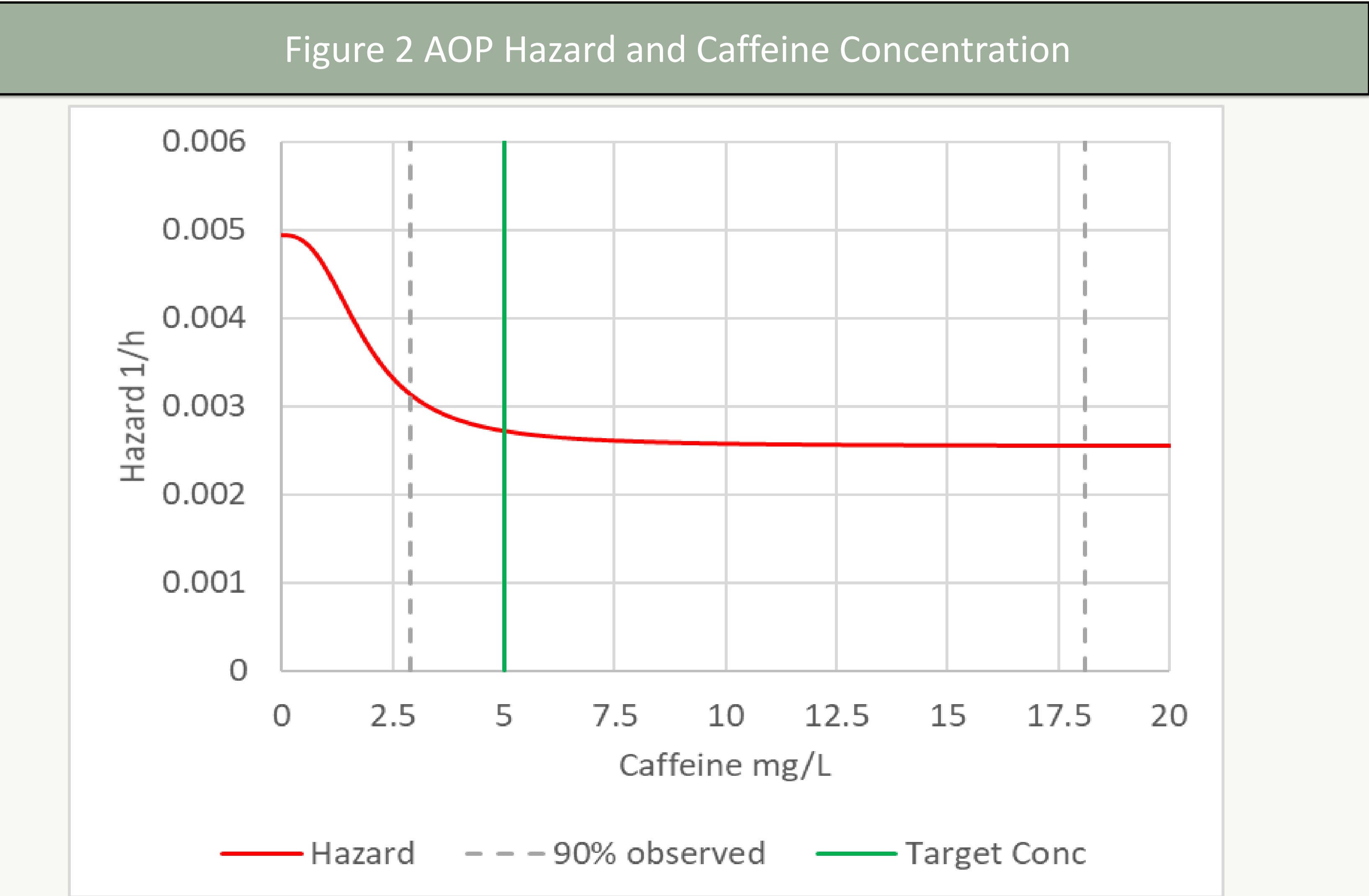
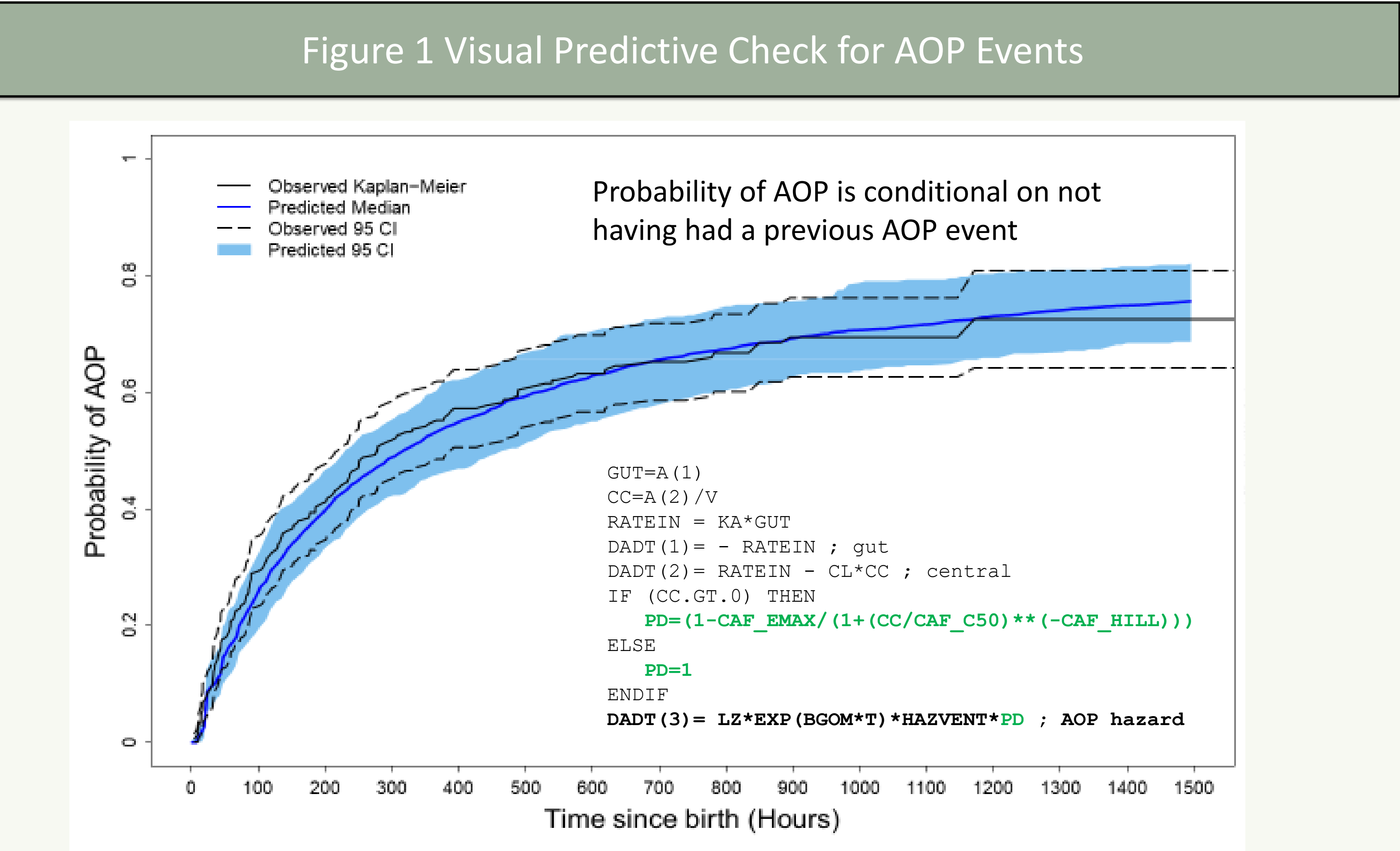
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References

Yang Y, Holford N, Jiang Z, Shen H, Shi J, Shu X, et al. A Population Pharmacokinetic Study of Caffeine Citrate in Chinese Premature Neonates. 20th PAGANZ, Auckland, 2019.

Table 1 Hazard Model Parameter Estimates

Description	Units	Original	Bootstrap average	2.5% ile	97.5% ile	RSE
Baseline hazard	1/h	0.00484	0.00494	0.00452	0.00564	6.5%
Gompertz hazard	.	0.00165	-0.00152	0.00206	-0.00122	16.9%
Emax for caffeine effect on hazard	1/h	0.512	0.483	0.427	0.522	4.0%
C50 for caffeine effect on hazard	mg/L	1.87	1.87	1.46	2.33	9.2%
Hill exponent for effect on hazard	.	2.50	2.59	2.31	2.71	4.6%
Fraction of C50 with A2A GG genotype	.	0.986	0.971	0.797	1.09	6.3%
Population parameter variability for LZ	.	0.801	0.831	0.700	0.904	6.9%
C50 with A2A receptor GG genotype	mg/L	1.84	1.82	1.42	2.24	12.3%
Gompertz half-life for baseline hazard	week	2.50	2.72	2.00	3.38	.



Conclusions

1. The hazard of AOP in premature neonates decreases from birth with a half-life of 2.7 weeks.

2. Caffeine can reduce the hazard of AOP by just over 50%.

3. A target caffeine concentration of 5 mg/L produces close to the maximum reduction of AOP hazard.

4. Dose individualization to achieve the target caffeine concentration can be obtained using NextDose (<https://www.nextdose.org>).