A closer look on neural inertia during anesthesia with different drug combinations in a controlled step-up/step-down design in humans

Kuizenga M.H.[1], Colin P.J.[1,2], Vereecke H.E.M.[1,3], Struys M.M.R.F.[1,2]

1. University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.
2. Ghent University, Ghent, Belgium.
3. AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium.

Background

- Neural inertia (NI) is defined as the tendency of the central nervous system to resist transitions between arousal states, potentially observable as a hysteresis in clinical signs and during neurophysiologic monitoring between induction and recovery
- This phenomenon has been observed in mice and *drosophila* with volatile anesthetics by demonstrating a higher required anesthetic concentration during induction than during recovery to switch between states (induction C_{50} > recovery C_{50}) (1)

Goal of Study

To evaluate this phenomenon in humans using propofol or sevoflurane (both with or without remifentanil) as anesthetic agents.

Materials & Methods

- 36 healthy volunteers received four sessions of anesthesia with different drug combinations in a step-up/step-down design
- During these sessions propofol or sevoflurane was administered with or without remifentanil (0, 2 or 4 ng mL^{-1})
- Serum concentrations of propofol and remifentanil were measured from arterial blood samples in steady state conditions
- Loss and return of responsiveness (LOR-ROR), response to pain (PAIN), Patient State Index (PSI) and 95% spectral edge frequency (SEF) were recorded and modeled with NONMEM to fit a sigmoidal E_{max} dose response relationship incorporating the fit of neural inertia

Ce_{REMI}	0 ng mL^{-1} (Group P & S)	2 ng mL^{-1} (50% of Group PR & SR)	4 ng mL^{-1} (50% of Group PR & SR)
Age (Years)	Males/Females	Males/Females	Males/Females
18-35	6/6	3/3	3/3
35-50	6/6	3/3	3/3
50-70	6/6	3/3	3/3
Total number Males/Females	18/18	9/9	9/9

Table 1. Stratification of 36 volunteers according to age, gender and remifentanil effect-site concentration (Ce_{REMI}).

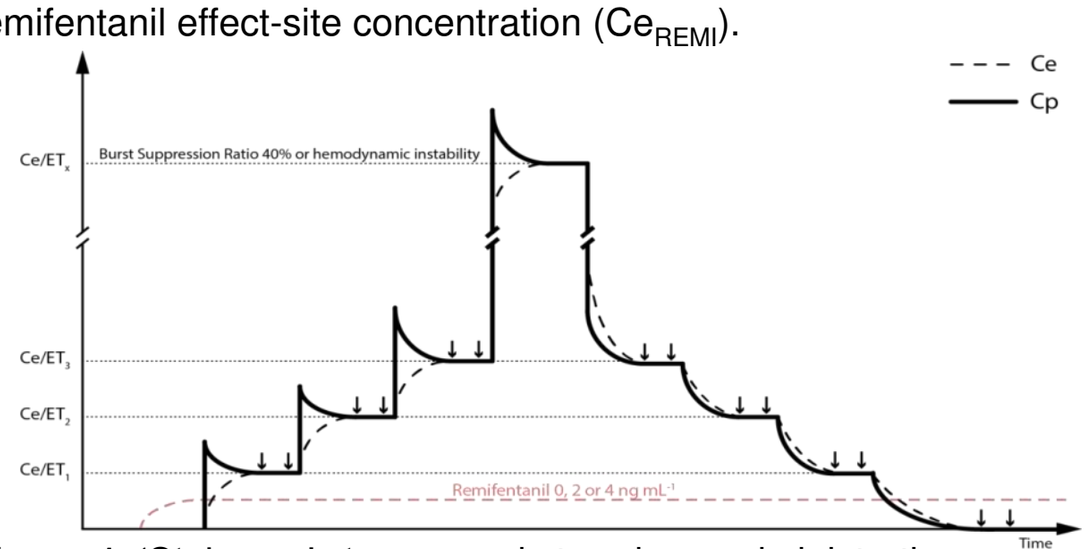

Figure 1. 'Staircase' step-up and step-down administration.

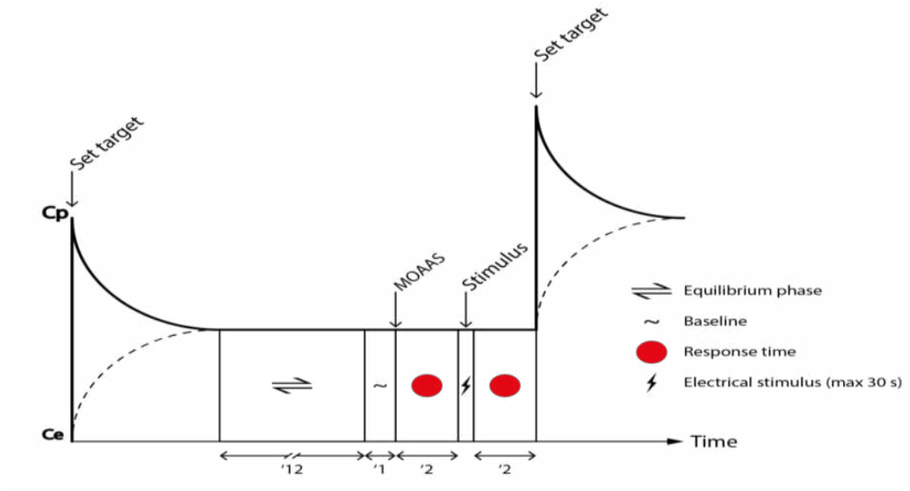

Figure 2. Observations of responsiveness in pseudo-steady state.

Results & Discussion

		LOR-ROR		PAIN		PSI		SEF	
		Prop	Sevo	Prop	Sevo	Prop	Sevo	Prop	Sevo
Baseline	E_0	-	-	-	-	84.6 (0.8)		21.2 (2.3)	
Drug effect	E_{max}	-	-	-	-	-65.0 (1.9)		-12.4 (4.9)	-11.3 (5.5)
	C_{50}	1.72 (5.4)	0.662 (6.0)	2.78 (12.7)	0.825 (9.3)	1.76 (5.1)	1.02 (4.6)	2.36 (5.7)	1.44 (6.8)
	γ	5.17 (12.8)	6.55 (12.2)	2.53 (10.9)	3.34 (9.8)	2.97 (5.2)		3.59 (12.8)	
	Slope	-	-	-	-	-	-	-	-
Remi inter-action	θ_1	-0.28 (15.4)	-0.23 (27.7)	-0.669 (7.7)	-0.543 (11.5)	-0.22 (14.7)	-0.17 (30.0)	-0.37 (14.3)	-0.11 (62.5)
	θ_2	0.77 (40.4)	0.88 (59.8)	0.24 (38.6)	0.31 (54)	NS	NS	NS	NS
Neural inertia	θ_3	NS	NS	NS	NS	NS	0.125 (34.1)	NS	NS
	θ_4	NS	0.184 (40.3)	NS	NS	NS	0.343 (29.1)	NS	NS
	θ_5	NS	0.402 (41.3)	NS	0.599 (43.6)	NS	NS	NS	NS
IIV	E_0^1	-	-	-	-	-	-	8.38 (34.3)	
	C_{50}^1	20.6 (37.2)	18.5 (42.1)	52.9 (30.9)	27.1 (37.8)	24.3 (24.0)	20.9 (33.9)	36.2 (29.6)	33.9 (55.1)
	ρC_{50}	0.81 (40.9)		0.67 (43.3)		0.72 (33.5)		0.85 (45.2)	
RUV	$\sigma_{Additive}$	-	-	-	-	9.53 (11.1)		3.52 (9.2)	

Table 2. The model parameters (E_0, E_{max},C_{50}, γ) for the various pharmacodynamic endpoints (LOR-ROR, PAIN, PSI, SEF) related to the measured concentration of propofol or sevoflurane in pseudo-steady state condition (C), the influence of remifentanil 2 ng mL^{-1} (θ_1) and 4 ng mL^{-1} (θ_2), and possible neural inertia on the model. More specifically, θ_3, θ_4 and θ_5 estimate the increase in C_{50} for the induction phase as compared to the recovery for the 0, 2 or 4 ng mL^{-1} remifentanil groups, respectively.

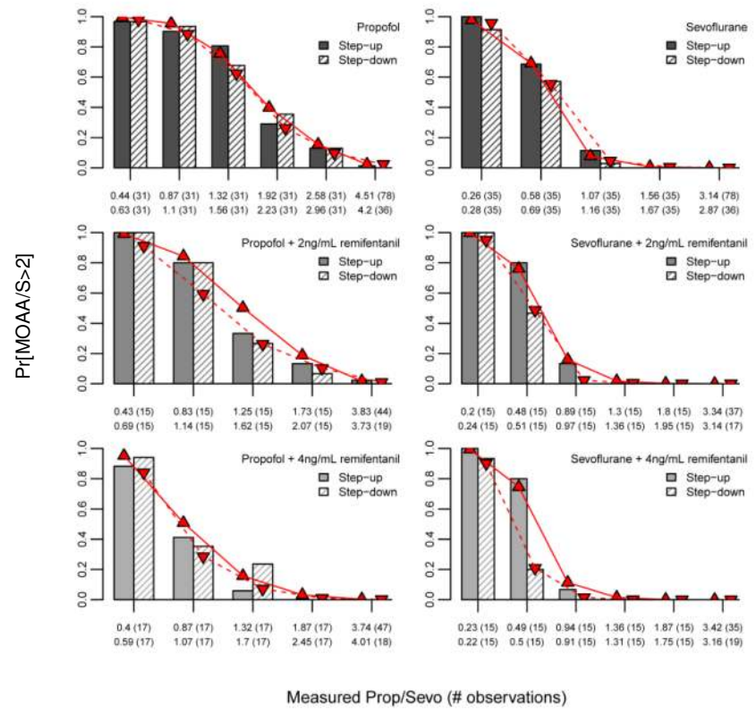

Figure 3. Barplots of the observed and predicted responses to a verbal command (LOR-ROR).

Conclusions

- Our results nuance the earlier findings with volatile anesthetics in mice and *drosophila*
- Methodological aspects of the study, such as the measured endpoint, have an effect on the detection of NI
- A more thorough definition of NI, accompanied by a robust methodological framework for clinical studies is required to advance our knowledge of this phenomenon

References

(1) Friedman EB, Sun Y, Moore JT, Hung H, Meng QC, Perera P, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia. PLoS ONE 2010;5(7):e11903