Pharmacodynamic interaction of remifentanil and dexmedetomidine on depth of sedation and tolerance of laryngoscopy

M.A.S. Weerink *et al.*

Supplemental Digital Content 3 -

A) *Simulation study to develop initial trial design*

B) *Adaptive trial design - Dexmedetomidine concentration adjustments*

C) *Adaptive trial design - Remifentanil concentration adjustments*

A) Simulation study to develop initial trial design

Clinical trial design is of crucial importance when studying the interaction between different drugs. Design elements such as (i) the number of volunteers to include, (ii) the dose levels of the different drugs and (iii) the sequence of drug administration are of particular importance and can, if chosen poorly, result in an uninformative clinical trial.

Therefore, in an attempt to maximize the efficiency of this trial, a simulation study was set up. This study aimed to compare various clinical trial designs which are described in literature or were used in the past in our institution to evaluate drug-drug interactions. Furthermore, we sought to optimize the aforementioned design aspects, thereby striking a balance between the theoretical optimal design and the design associated work-load/costs.

In short, for these simulations we assumed a synergistic interaction between dexmedetomidine and remifentanil in line with what was found for the interaction between propofol and remifentanil, with a remifentanil EC_{50} of 1.36 ng/ml.[1,2] Moreover, we assumed that the effect-site concentration of dexmedetomidine necessary to induce tolerance of laryngoscopy (TOL) in 50% of volunteers was 4.0 ng/ml. This value was deduced from the work of Kunisawa *et al*.[3] described 5 cases of awake intubation under sedation using dexmedetomidine. The different trial designs were simulated 1000 times and the bias and precision of the parameter estimates obtained from fitting a hierarchical interaction model to the simulated data were compared. Besides metrics based on parameters estimates, the determinant of the Fisher Information Matrix, known as the “D-optimality criterion” in optimal design theory, was used to compare designs.

Based on a feasible 60 study sessions, various clinical trial designs and subsequent modifications of these designs were evaluated and compared. Among these were a design in line with our previous trial in combinations of propofol, sevoflurane and remifentanil were assessed,[4] and the criss-cross design as proposed by Short *et al.*[5]

These analyses showed that DESIGN 5, best suited our purpose to obtain a reliable estimate of the magnitude of the interaction and the variability in the response to the dexmedetomidine-remifentanil combinations. According to this selected design, age- and sex-stratified volunteers receive a “step-up” dexmedetomidine dosing regimen during session 1. During this “step-up” titration, target controlled infusion (TCI) is used to target effect site concentrations of 1, 2, 3, 5 and 8 ng/ml dexmedetomidine. In session 2, after an appropriate washout (> 1 week), these volunteers receive a dexmedetomidine infusion targeting an effect site concentration of 2 ng/ml. After an appropriate equilibration time, remifentanil is administered by “step-up” titration targeting effect site concentrations of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 ng/ml. In these groups effect-site TCI, based on our based on our previously published model is used to target dexmedetomidine concentrations and our recently published Eleveld PKPD model is used to target remifentanil concentrations.[6–8]

Additionally, a remifentanil phase was added to the study protocol, to be able to validate the previously published Eleveld PKPD model for remifentanil.

Table S3.1. Comparison of various trial designs by stochastic simulations

	DESIGN 1	DESIGN 2	DESIGN 3	DESIGN 4	DESIGN 5
	5 optimized DMED steps	2 crossover groups	4 independent groups	Criss-cross	Crossover with 1 DMED and 1 REMI step-up session
Subjects	30	30	60	60	30
Sessions per subject	2	2	1	1	2
Sessions total	60	60	60	60	60
Dose levels					
DMED step-up (ng/ml)	1, 3, 4, 5, 8 0.5, 2.0, 3.0, 4.0, 6.0 0.5, 1.0, 1.5, 2.0, 4.0 0.5, 0.75, 1.0, 1.25, 2.0			1, 3, 4, 5, 8 *	
Fixed REMI concentration (ng/ml)	0 (n=30) 0.5 (n=10) 2.0 (n=10) 4.5 (n=10)	0 (n=15) 0.5 (n=15) 2.0 (n=15) 4.5 (n=15)		0 (n=6) 1 (n=6) 3 (n=6) 4 (n=6) 5 (n=6)	0 (n=30)
REMI step-up (ng/ml)	-	-	-	0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 **	
Fixed DMED concentration (ng/ml)	-	-	-	0 (n=6) 1 (n=6) 2 (n=6) 3 (n=6) 4 (n=6)	2 (n=30)
Estimated CV% (p95 (%))					
EC50_DMED	10	12	15	16	9
EC50_REMI	31	34	48	44	21
Gamma_O	30	23	36	26	26
Gamma	18	17	19	20	20
IIV_EC50_DMED	64	58	57	64	54
IIV_EC50_REMI	-	-	-	-	-
Shrinkage (p95 (%))					
IIV_EC50_DMED	30	29	40	45	21
IIV_EC50_REMI	-	-	-	-	-
D-opt crit (p5)	2.8e6	3.9e6	6.1e5	1.1e6	9.1e6

*In DESIGN 4, *50% reduced for 2 highest REMI groups **50% reduced for highest 2 DMED groups.*
DMED = Dexmedetomidine, REMI = Remifentanil, CV = coefficient of variation, EC50 = half maximal effective concentration, IIV = inter-individual variability, D-opt crit = D-optimality Criterion

B) Adaptive trial design - Dexmedetomidine concentration adjustments

The initial dexmedetomidine schedule is based on the assumption that the EC50 for TOL will be approximately 4 ng/ml. This assumption is based on a study by Kunisawa *et al*.[3] describing an EC50 of 4 ng/ml for TOL. As their study focused on dexmedetomidine for awake fiberoptic intubation, it would be inappropriate to just extrapolate their findings. Therefore an interim analysis was planned after 5 volunteers. If volunteers would be tolerating a laryngoscopy with much lower or higher concentrations than expected, the targeted concentrations would be adjusted as pointed out in figure S3.1 and table S3.2 below. Thereby ensuring the most informative study design.

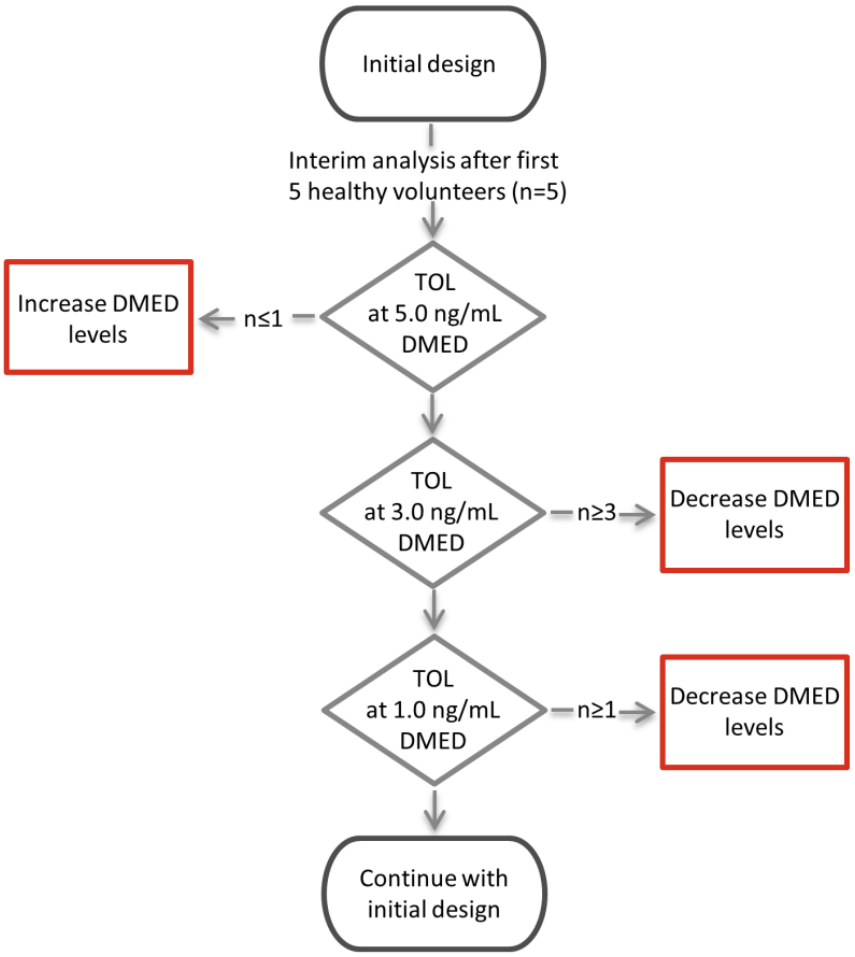

Figure S3.1 Flow diagram of interim analysis and dexmedetomidine (DMED) adjustments. TOL = tolerance of laryngoscopy

Table S3.2 Probability (%) of observing {0, 1 …5} subjects tolerating a laryngoscopy (N TOL) at a DMED concentration of 1.0, 3.0 and 5.0 ng/ml

N TOL	DMED					
	0.0	1.0	3.0	4.0	5.0	8.0
0		99	36		< 0.1	
1		*0.3*	*40*		*1.2*	
2		< 0.01	18		7.8	
3		< 0.01	4		25	
4		< 0.01	0.4		40	
5		< 0.01	< 0.1		25	

C) Adaptive trial design - Remifentanil concentration adjustments

The initial remifentanil schedule is based on the assumption that 50% of the patients will be TOL at an effect site concentration of 1.36 ng/ml remifentanil, when a dexmedetomidine background concentration of 50% the $EC50_{TOL}$ is present (remifentanil EC50 = 1.36 ng/ml). A similar synergistic interaction between remifentanil and dexmedetomidine as between remifentanil and other hypnotic agents was assumed. The value of 1.36 ng/ml is based on values from previous studies regarding the interaction between remifentanil, sevoflurane and propofol.[2,9]

After 5 subjects it was re-evaluated whether this assumption seemed right. If volunteers would be tolerating a laryngoscopy with much lower or higher concentrations than expected, the targeted concentrations would be adjusted (halved or doubled) as pointed out in the figure below and tables S3.3 and S3.4. Hereby ensuring that the most informative concentration range is studied.

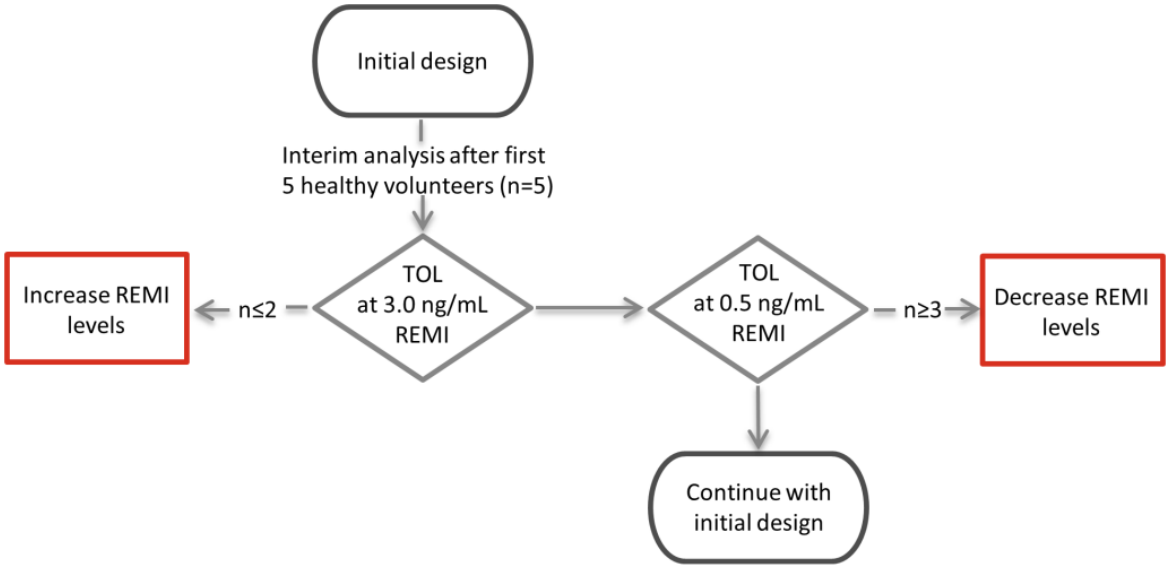

Figure S3.2 Flow diagram of interim analysis and remifentanil (REMI) adjustments. TOL = tolerance of laryngoscopy

Table S3.3. Expected number (percentage) of subjects tolerating a laryngoscopy at various concentrations (ng/ml)

DMED	REMI							
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	4.0
2.0	1 (2.6)	4 (12)	10 (32)	17 (56)	22 (75)	26 (86)	28 (92)	29 (97)

Table S3.4. Probability (%) of observing {0, 1 …5} subjects tolerating a laryngoscopy (N TOL) at REMI concentrations of 0.5 and 3.0 ng/ml REMI with a DMED concentration of 2.0 ng/ml

N TOL	REMI							
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	4.0
0		52					< 0.01	
1		36					< 0.1	
2		10					0.4	
3		1					5	
4		<0.1					29	
5		<0.01					66	

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