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Remimazolam exposure-response relationship model for sedation depth suggests influence of its main metabolite by competitive antagonism

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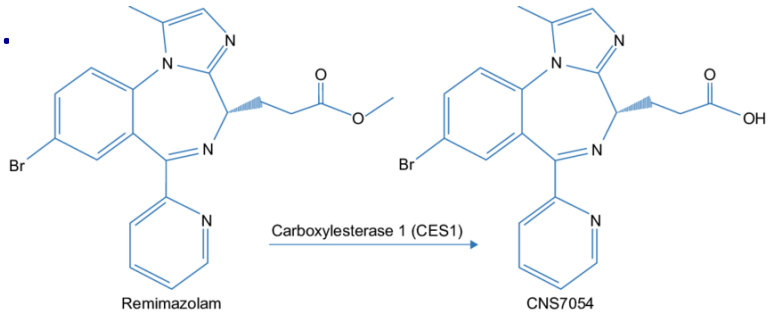
Background

- Remimazolam (Byfavo, Paion), is a benzodiazepine with a sedative effect.
- Remimazolam is rapidly hydrolyzed by CES1A (which is mainly present in the liver) in CNS7054, the main metabolite.
- We report on the exposure-response relationship for remimazolam for depth of sedation as measured by MOAA/s and the influence of CNS7054.

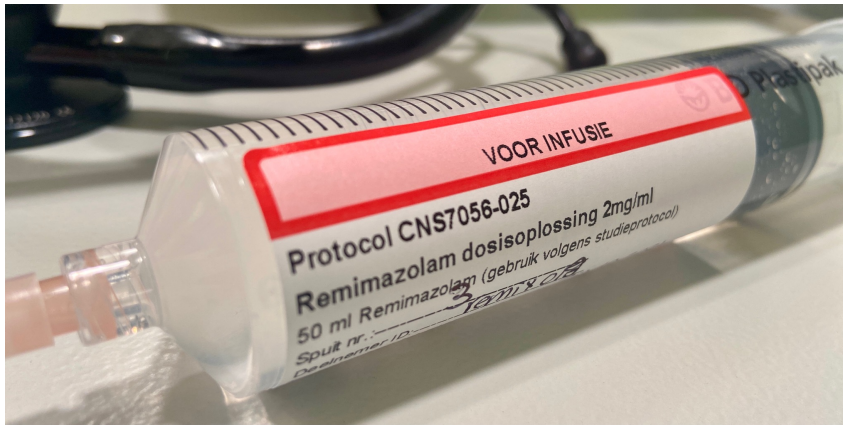


Methods I

- 24 healthy volunteers, stratified by age (3 groups) and sex, were included.

- Remimazolam was dosed in a step-up and step-down scheme using target controlled infusion to effect side concentrations from 150 to 2000 ng mL^{-1}.

- Target concentrations were optimized based on interim modelling results of remimazolam PK/PD from PAION and Schüttler and colleagues[1].



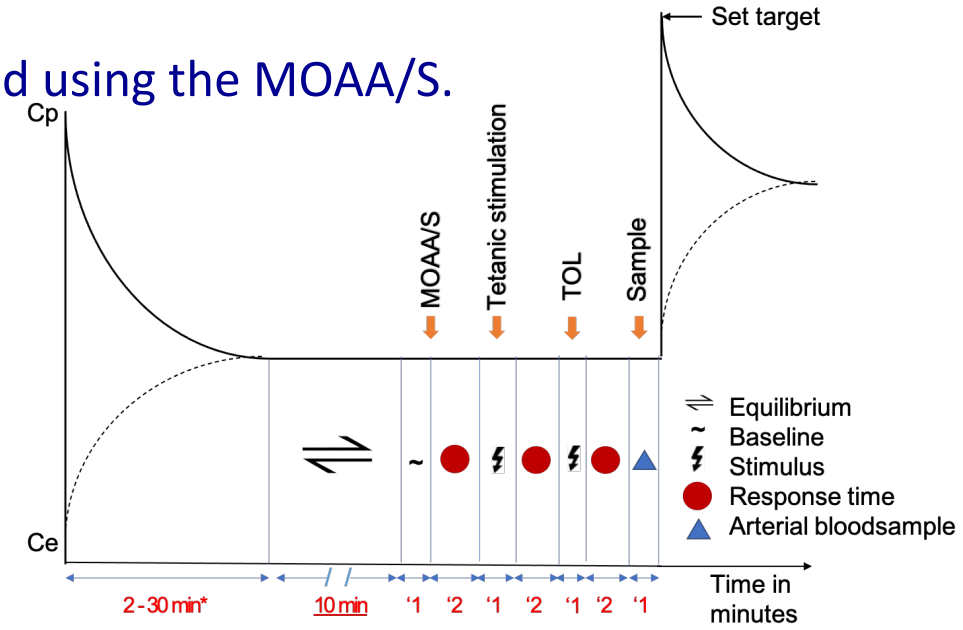
1. Schüttler, J. *et al.* Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers Part I. Pharmacokinetics and Clinical Pharmacodynamics. *Anesthesiology* **132**, 636–651 (2020).

Methods II

- Arterial samples were drawn at pseudo steady state after a minimum equilibration period of 25 min after target adjustment

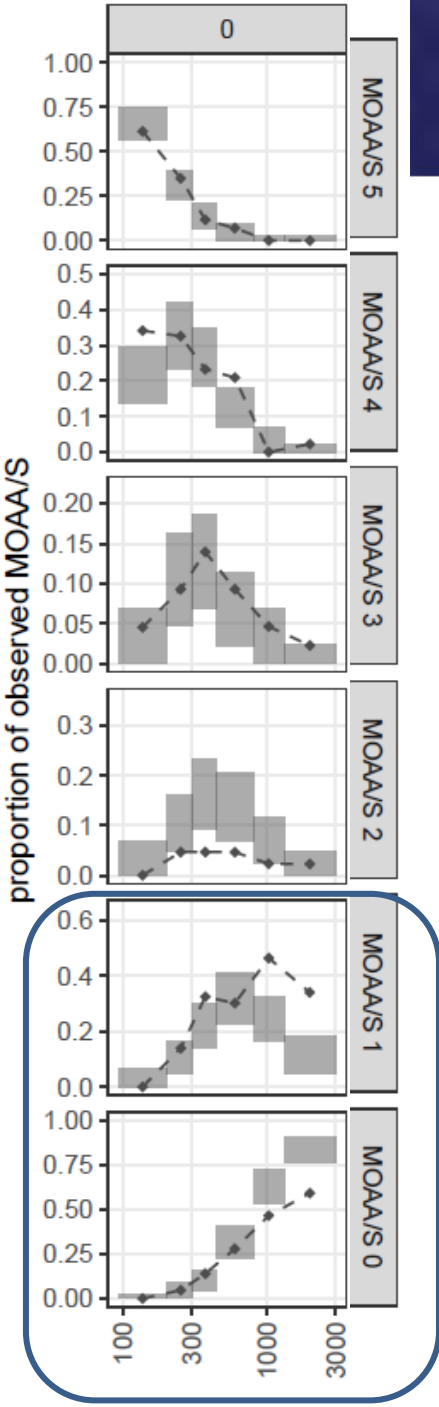
- The exposure-response relationship was modelled using mixed-effects proportional odds logistic regression (POLR) model in NONMEM.

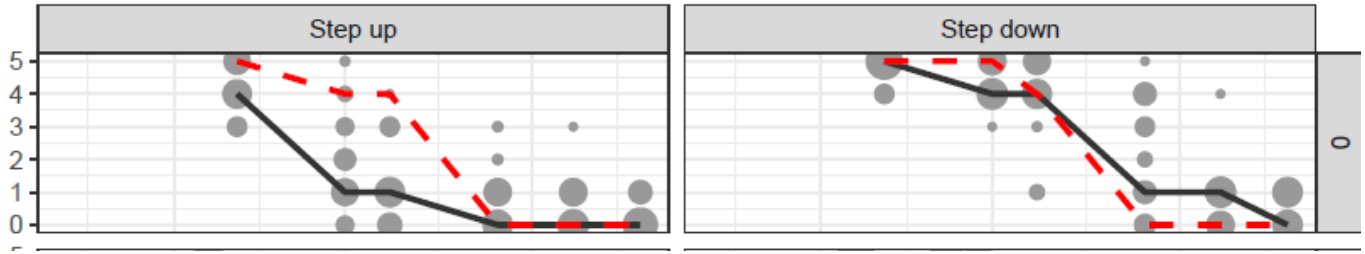
- Depth of sedation was measured using the MOAA/S.



Results

- VPC (visual prediction check) shows poor fit for lower MOAA/s scores.
- The POLR model failed to describe our observed data.
- Most notably, the model did not describe the difference in observed MOAA/s between the step-up and step-down sequence in our trial.

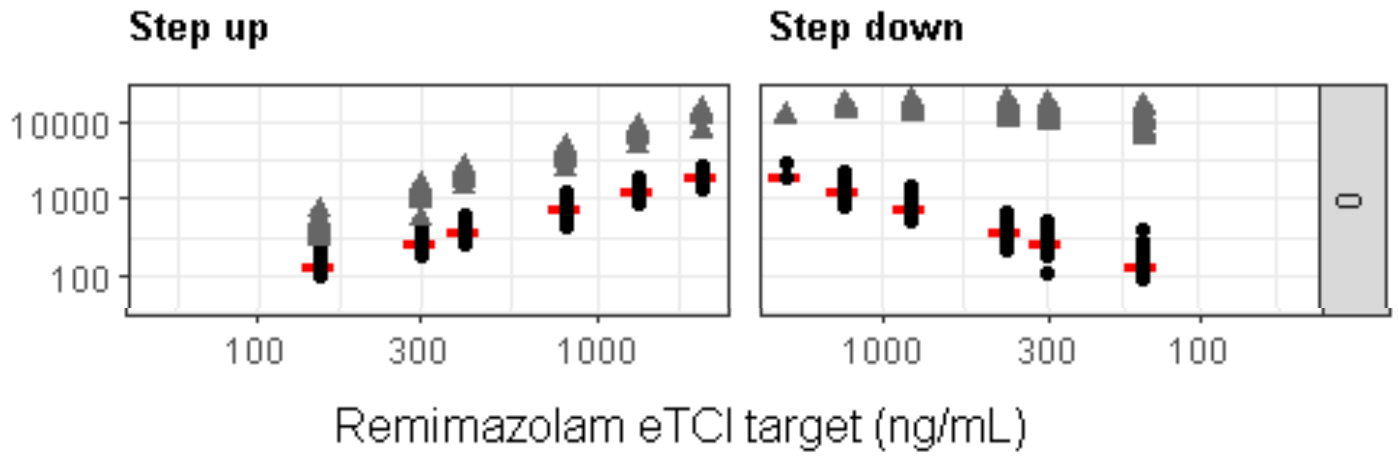




Black lines show most frequently observed Moaa/s

Red lines show the predicted Moaa/s based on POLR model.

Is TCI performance the problem ?

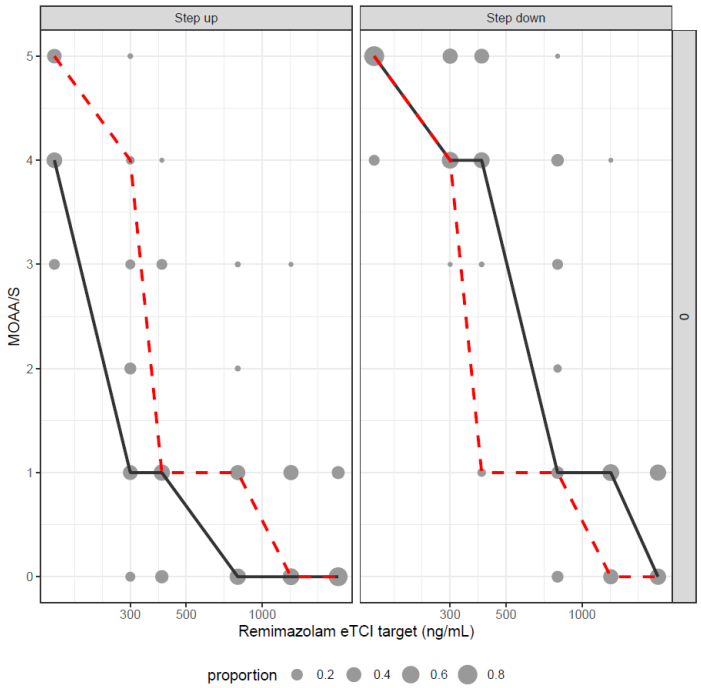


CNS7054 : remimazolam ratio increased from 2.9 to 63.4 for the 150 ng.mL-1 target in the step up vs. the step down sequence respectively

Red lines are target concentrations and the **grey bars** are the concentrations of CNS7054

Effect of the ”inactive” metabolite?

Model proposed by Holford and Sheiner[2] ,that accounts for competitive interaction between two ligands at the same receptor.



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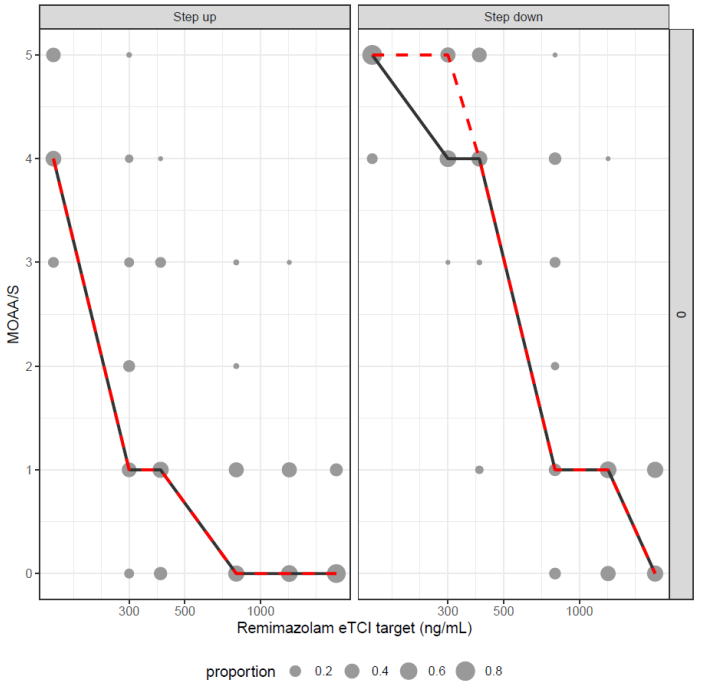


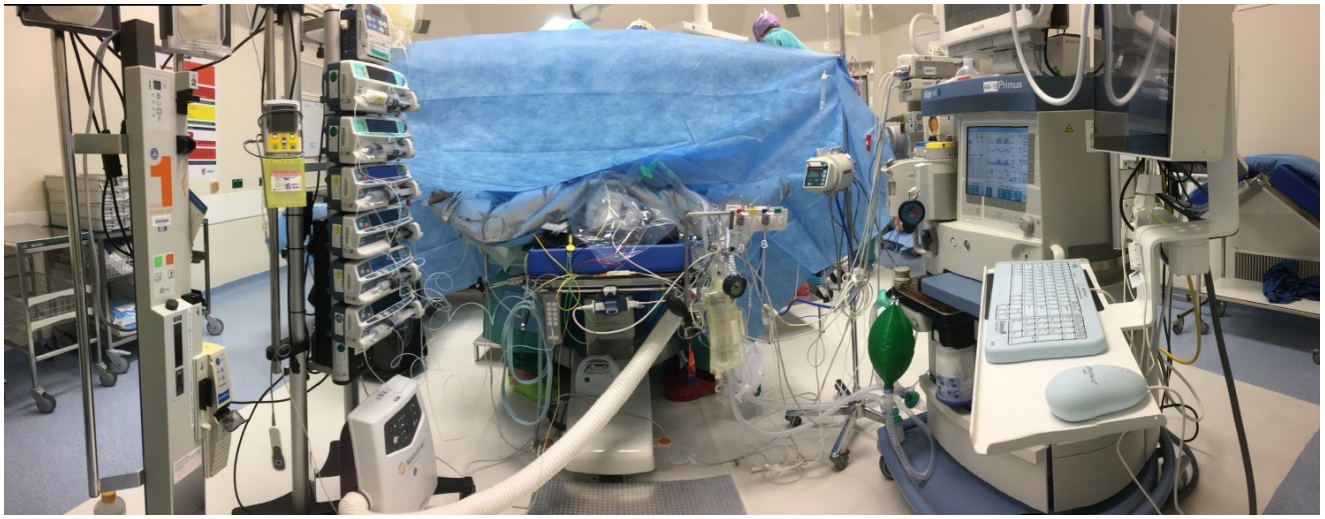
Black lines show most frequently observed Moaa/s
Red lines show the predicted Moaa/s based POLR.

2. Holford, NHG and Sheiner LB (1982) Kinetics of pharmacologic response. Pharmacol Ther 16:143–166 (1982)

Results III

- The model predicted CNS7054 is a weak agonist with a maximum effect on MOAA/S 15-fold lower than remimazolam.

- At the same time, half of the maximum effect for remimazolam is reached around 210 ng.mL-1 whilst for CNS7054 the IC50 is 10-fold higher at around 2465 ng.mL-1.



Conclusion

- We found a significant difference in the depth of sedation for identical effect-site target concentrations between the step-up and step-down sequence.
- In our study, CNS7054 concentrations accumulated with increasing infusion duration.
- A model accounting for competitive antagonism between remimazolam and CNS7054 accurately described the higher MOAA/S in the step down vs. the step-up part.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