Leveraging PRC to Guide Remimazolam Dosing for Sedation

Introduction

Remimazolam in a novel short-acting benzodiazepine recently approved in the United States for procedural sedation[1] but has a clinically significant failure rate at achieving adequate sedation (8.7-19.4%)[2-3]. We have previously demonstrated that the use of PRC to identify the dose of propofol required for sedation results in a decrease in the variability in target effect[4], and PRC has been successfully used in DISE procedures[5], as well as endoscopies. Briefly, PRC identifies a target effect site concentration required to achieve a clinical outcome and then determines how to maintain that target. We hypothesize that applying the PRC algorithm would result in more consistent and successful dosing with less significant adverse effects. We tested this hypothesis recognizing the incomplete pharmacokinetic profile of the drug and assuming for a large population heterogeneity.

Methods

Using MATLAB, we performed a Monte Carlo simulation of 20000 patients receiving remimazolam as a single agent in a 60-minute window in order to achieve and then maintain moderate sedation (OAA/S 2-3) while avoiding deep sedation (OAA/S 1). The pharmacokinetic parameters (volumes and clearances) as well as the pharmacodynamic parameters (ke0 and clinical effect) were randomly assigned such that the parameters would fall within the 5th and 95th percentile of their estimated value[6].

Each patient was simulated under three conditions:

1) Following the product monograph: 5 mg bolus initially and then 2.5 mg boluses thereafter at a rate not to exceed once every 2 minutes[1]
2) Using the original PRC algorithm[4] to identify a target effect site concentration followed by a series of infusions so that the effect site concentration remains within 5% of the target value. If the patient became over- or under-sedated the algorithm would adjust the target effect site concentration accordingly.
3) An updated version of the PRC algorithm followed by the same adjustments described above.

Results

Figure 1 demonstrates an example of the simulated effect site concentration over time in the three conditions described previously. Table 1 shows the compiled results of all simulations. Briefly, the bolus technique failed to achieve therapeutic levels in approximately 5% of cases and took more than 10 minutes in over 25 % cases; PRC achieved adequate sedation in all cases within 15 minutes. While the PRC algorithm had more patients achieving deep sedation, this was primarily at the transition from target identification to target maintenance. Of note, the bolus technique yielded deep sedation for a longer of period of time. The second version of PRC resulted in a faster overall target identification time compared to the original PRC algorithm at the cost of more overshoot.

Conclusion

The simulation study demonstrates that PRC can appropriately titrate remimazolam despite an incomplete pharmacokinetic profile. The failure rate identified in this simulation study appears to mimic the clinical failure rate with fentanyl being used to augment sedation in the clinical studies. Clinical evaluation of the PRC algorithm is required for final validation and will allow for further tuning of the algorithm.

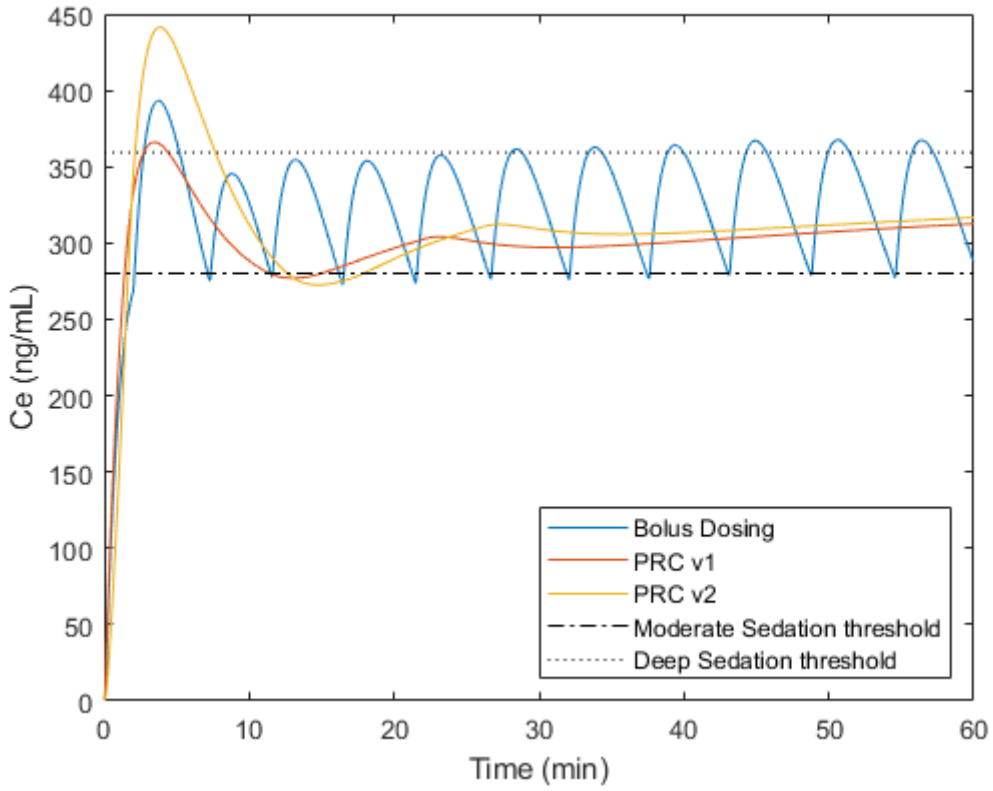

Figure 1: Example of a simulated patient's remimazolam effect site concentration after either Bolus dosing or using the PRC algorithm

N = 20000	Bolus	PRC	PRC v2
Number of patients failed to reach target (%)	951 (4.8%)	0	0
Number who took more than 10 min to reach target (%)	5206 (26 %)	247 (1.2%)	22 (0.1 %)
Average target time (min) (std)	9.16 (9.94)	4.91 (2.83)	2.65 (0.93)
Average time above threshold (min) (std)	48.12(10.53)	50.64 (4.21)	52.51(3.52)
Number of patients over-sedated (%)	5527 (27.6)	10662 (53.3)	13684 (68.2)
If over-sedated, amount of time over-sedated (min) (std)	24.9 (17.72)	6.55 (5.32)	8.02 (5.64)
Median number of doses to achieve a target (50% (25-75, 100))	18 (14-23, 30)	N/A	N/A
Median number of redoses if solution found (50% (25-75, 100))	14 (12-16, 22)	N/A	N/A
Median number of adjustments to titrate PRC once target found (50% (25-75,100))	N/A	3 (0-5, 22)	4 (2-6, 23)

Table 1: Compiled results of Monte Carlo Simulation comparing Bolus dosing with both PRC implementation

References

1. Acacia Pharma I. BYFAVO™ (remimazolam) [package insert]. *US Food and Drug Administration website*. 2020;

2. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest*. Jan 2019;155(1):137-146. doi:10.1016/j.chest.2018.09.015
3. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. Sep 2018;88(3):427-437.e6. doi:10.1016/j.gie.2018.04.2351
4. Mandel JE, Sarraf E. The Variability of Response to Propofol Is Reduced When a Clinical Observation Is Incorporated in the Control: A Simulation Study. *Anesthesia & Analgesia*. 2012;114(6)
5. Atkins JH, Mandel JE, Rosanova G. Safety and efficacy of drug-induced sleep endoscopy using a probability ramp propofol infusion system in patients with severe obstructive sleep apnea. *Anesth Analg*. Oct 2014;119(4):805-10. doi:10.1213/ane.0000000000000229
6. Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers. *Anesthesiology*. 2020-04-01 2020;132(4):636-651. doi:10.1097/aln.0000000000003103