Remimazolam: A Retrospective Study of Initial Safety and Efficacy Data in Diverse Procedural Sedation

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BACKGROUND

- Remimazolam (Byfavo™) is a new ultra-short acting benzodiazepine the Food and Drug Administration (FDA) approved in 2020 for adults undergoing short procedural sedation (<30 minutes) with dosing based on a patient's ASA-PS score
- Designed as a "soft drug," the organ-independent metabolism of remimazolam offers a pharmacokinetic and pharmacodynamic advantage, making it a safer and more efficient option for sedation[1,2]
- Remimazolam is rapidly hydrolyzed by esterases in the liver and tissues to inactive metabolites allowing for a smaller volume of distribution, shorter half-life, and increased clearance[3,4]
- Remimazolam offers a significantly reduced recovery time compared to midazolam[5-7] and greater hemodynamic and respiratory stability compared to propofol[8,9,1]
- Current research is limited to pharmaceutical industry funded RCTs with no real-world utilization studies.
- The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board as exempt.
- Associations between recovery time, adverse effects, and dose-response within various patient groups receiving remimazolam will support the creation of a nurse procedural sedation protocol with non-ASA-PS dosing guidelines

AIMS

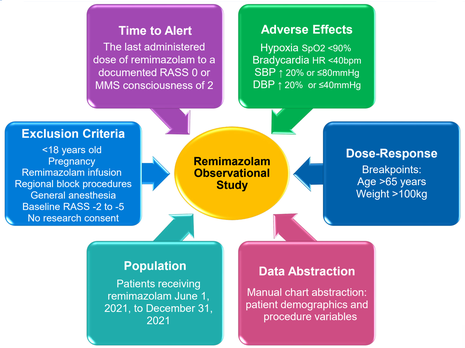
Primary Aim

- To evaluate factors affecting variability in time to alert and adverse effects in response to remimazolam during procedural sedation

Secondary Aim

- To evaluate dose-response in various patient groups (i.e., age >65yrs, weight >100kg)

METHODS



Statistical Analysis

- Continuous variables were compared between medication groups using either t-tests or Kruskal-Wallis tests for continuous data and either Chi-square or Fisher's exact tests for categorical data
- Univariate and multivariable linear regression were used to assess the association of patient and clinical characteristics with time to alert
- Logistic regression assessed the association of patient and clinical characteristics with adverse effects
- Spline plots used to assess the functional form of the relationships between continuous variables and adverse events for breakpoints of the continuous variables to predict an adverse event

FDA DOSING GUIDELINE

ASA 1 and 2

- 5 mg IV with supplemental doses of 2.5 mg IV every 2 minutes as indicated

ASA 3 and 4

- 2.5 mg to 5 mg IV with supplemental doses of 1.25 mg to 2.5 mg every 2 minutes as indicated (dose based on general condition of patient and provider discretion)

RESULTS

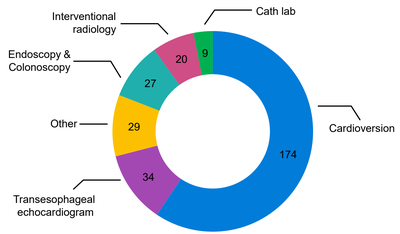
DEMOGRAPHICS

	Total (N=292)
Age (years)	68.3 ± 12.6
Gender	
Male	180 (61.6%)
Female	112 (38.4%)
Body mass index, kg/m²	29.8 ± 7.2
ASA-PS	
1, 2	41 (14.0%)
3-5	251 (86.0%)
Comorbidity, OSA	87 (29.8%)
Reversal agent given	1 (0.3%)
Any adverse effect	81 (27.7%)
Hypoxia	41 (14.0%)
Systolic hypertension	39 (13.4%)
Systolic hypotension	21 (7.2%)
Diastolic hypotension	9 (3.1%)
Bradycardia	5 (1.7%)

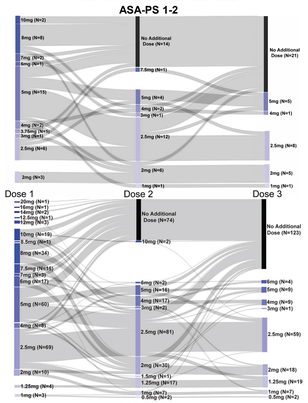
PROCEDURAL CHARACTERISTICS

	Remimazolam alone (N=187)	Remimazolam + Fentanyl (N=20)	Remimazolam + Propofol (N=62)	Remimazolam + Other/Combo (N=23)	p-value
Procedure					<0.001
Cardioversion	152 (81.3%)	3 (15.0%)	19 (30.6%)	0 (0.0%)	
TEE	5 (2.7%)	6 (30.0%)	18 (29.0%)	5 (21.7%)	
Other	13 (7.0%)	6 (30.0%)	5 (8.1%)	5 (21.7%)	
Endoscopy/Colonoscopy	6 (3.2%)	3 (15.0%)	13 (21.0%)	5 (21.7%)	
Interventional Radiology	10 (5.3%)	2 (10.0%)	5 (8.1%)	3 (13.0%)	
Cath lab	1 (0.5%)	0 (0.0%)	2 (3.2%)	5 (21.7%)	
Remimazolam total dose, mg	8 (6, 12)	12.5 (8, 20)	15 (10, 20)	20 (7.5, 20)	<0.001
Hemodynamic agent given	5 (2.7%)	2 (10.0%)	8 (12.9%)	5 (21.7%)	<0.001
Anesthesia length, minutes	21 (17, 31)	56 (33, 79)	40 (31, 57)	65 (39, 104)	<0.001
Any adverse effect	36 (19.3%)	5 (25.0%)	28 (45.2%)	12 (52.2%)	<0.001
Hypoxia	16 (8.6%)	3 (15.0%)	14 (22.6%)	8 (34.8%)	<0.001
Systolic hypertension	19 (10.2%)	3 (15.0%)	12 (19.4%)	5 (21.7%)	0.17
Systolic hypotension	6 (3.2%)	3 (15.0%)	8 (12.9%)	4 (17.4%)	0.005
Diastolic hypotension	2 (1.1%)	2 (10.0%)	3 (4.8%)	2 (8.7%)	0.032
Bradycardia	4 (2.1%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0.81

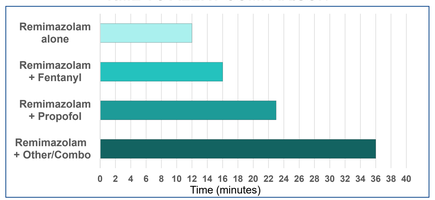
PROCEDURE TYPE



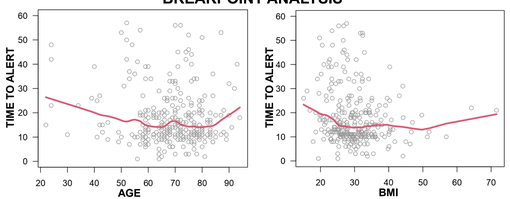
DOSING ADHERENCE



TIME TO ALERT COMPARISON



BREAKPOINT ANALYSIS



Multivariable model for time to alert

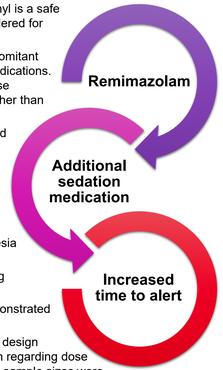
- After adjusting for age, gender, BMI, type of procedure, ASA-PS, and total dose of remimazolam given, we found a significant interaction between medications given and length of anesthesia
- Age, gender, type of procedure, ASA-PS, and total dose of remimazolam administered were not significant
- For every additional 10 minutes of anesthesia a patient received, the time to alert increased by an average of:
  - Remimazolam alone: 2.0 min (95% CI 0.6 to 3.3, p=0.005)
  - Remimazolam + Fentanyl: 0.4 min (95% CI -0.4 to 1.2, p=0.28)
  - Remimazolam + Propofol: 5.5 min (95% CI 4.3 to 6.8, p<0.001)
  - Remimazolam + Other/Combo: 2.4 min (95% CI 1.7 to 3.0, p<0.001)

Multivariable model predicting hypoxia

- Receiving additional sedation medications significantly increased odds of hypoxia (OR 2.77, 95% CI 1.30-5.91, p=0.008), after adjusting for BMI, ASA-PS, and total remimazolam dose
- There was a 25% increase in odds of experiencing hypoxia for every 5 kg/m² increase in BMI (95% CI 1.01-1.54, p=0.037)

DISCUSSION

- Remimazolam exhibited a higher safety profile when administered independently
- Remimazolam + Fentanyl had a lesser effect on time to alert than anticipated
- Our results indicate Remimazolam + Fentanyl is a safe pharmacological option and could be considered for nurse procedural sedation
- A significant cause of hypoxia was the concomitant use of remimazolam with other sedation medications. Data may lead the anesthesia provider to use remimazolam as a single sedative agent rather than a multi-sedative approach
- The risk of hypoxia in patients with increased BMI should be considered when dosing remimazolam
- We speculate the decision to use additional sedation medication was due to provider preference, procedure type, inexperience using remimazolam, or suboptimal sedation
- Providers should consider length of anesthesia as a factor in increasing time to alert
- An increased initial dose in short, stimulating procedures was noted
- No clear breakpoints in dose-response demonstrated appropriate dosing strategies by ASA-PS
- Limitations include the study's retrospective design and lack of provider feedback or explanation regarding dose selection and patient response. Additionally, sample sizes were limited within the additional sedation medication categories



CONCLUSIONS

- Remimazolam appears to offer ideal characteristics for a procedural sedation medication, with minimal hemodynamic and respiratory impact, quick recovery, and no residual sedative effects
- Future studies are needed to examine the cost comparison of using remimazolam versus midazolam and whether decreased recovery time offsets the increased cost
- Further investigation of remimazolam and fentanyl use within a nurse procedural sedation protocol would provide additional insight into the versatility of this drug

ABSTRACT AND REFERENCES