REMIMAZOLAM
ANOTHER ROAD TO ROME

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Disclosures

• No financial disclosures
• OFF-Label use of medication WILL be discussed
Drug Development:

- Phase I trials: 2012
- Phase II 2015
- Phase III: 2018

- Remimazolam approved for use in Japan 2020
  - Approved for use in US: July 2020
  - Approved for use in EU: March 2021

- First use at Mayo clinic: July 2021
PHARMACOLOGY
Remimazolam
Formulation

- 20mg lyophilized powder
- Reconstitute in saline 8.2mL - >2.5mg/mL
  - Real world: 20mg into 10mL = 2mg/mL
- For IV injection
- Reconstituted in vial: stable 8 hrs room temp
- Dosing:
  - ASA 1-2: 5mg IV with 2.5mg Q2min PRN
  - ASA 3+: 2.5mg with 1.25-2.5 Q2 PRN
Unusual Complications

IV compatibility

- Remimazolam forms precipitates in:
  - Lactated Ringer’s
  - Acetated Ringer’s
- Concentration 5mg/ml
  - US concentration 2-2.5mg/mL
Remimazolam:
Mechanism

- $\text{GABA}_A$ Ligand
  - Binds gamma subunit
  - Increases chloride flux
- Produces sedation

https://en.wikipedia.org/wiki/GABAA_receptor
Remimazolam: 
Physiochemical Properties

- Additional Ester linkage
- pH 2.9-3.9 in saline

![Remimazolam and Midazolam Structures](image)

Remimazolam: Metabolism

- Ester linkage hydrolyzed:
  - Tissue esterase
  - Carboxylesterase 1 (CES1)
    - Hepatic
- Inactive metabolite:
  - CNS 7054
Remimazolam
Formal Pharmacokinetics

• Volume of distribution: 34 ± 9.4L
• Terminal Half-life: 45min ±9min
• Clearance time independent of body mass
• Extremes of hepatic dysfunction: approx 30% increase in duration
Remimazolam
Practical pharmacokinetics

• Onset and offset:
  • 1-2 minutes for onset
  • Offset: dose dependent
    • roughly 10-12 minutes for an 8mg bolus
Remimazolam
Pharmacology: Bioavailability

• PO
  • 100% absorption as a liquid
  • 1.2% bioavailability PO

• Intranasal:
  • Bioavailability: 20-45%. (powder or solution)
  • Prohibitively painful to use intranasally

Procedural Use
Remimazolam
Procedural Uses

• GI endoscopy
  • LVAD patients
  • ALS PEG tube patients
  • Feeding tube w/ odynophagia

• Cardiac Cath Lab:
  • Cardioversion
  • Congenital Percutaneous interventions
  • Induction agent

• Interventional Radiology
  • vascular access w/ poor CV status
  • vascular stenting, angiography, PICC/HD catheter placement

• ultrasound guided procedures needing quick sedation
• - CT guided quicker procedures (bones biopsies, etc)

• Neurosurgical/ Neuro IR outpatient procedures:
  • - trigeminal ablations
Remimazolam
Procedural Advantages

• Very hemodynamically stable:
  • Minimal changes to SVR
  • Minimal Changes to HR
  • No rhythm disturbances

• Minimal respiratory depression
  • Spontaneous respiration preserved

• Rapid emergence

• Easily titrated due to short duration

• Reversible with flumazenil if needed
Remimazolam
Procedural Disadvantages

• Short duration = frequent dosing
  • Manage provider expectations
• IV compatibility issues
• $$
Conclusions:

- Pros and Cons: Context dependent
- Con: $
- Very titratable
- Reversible
- Quick wakeup with minimal grogginess

- Good hemodynamic profile
- Minimal respiratory depression when used as solo agent
Questions?

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# Sedation Protocol

<table>
<thead>
<tr>
<th>Remimazolam</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 5mg bolus</td>
<td>- 1.75mg + 1mg x2 if &lt;60yrs</td>
</tr>
<tr>
<td>- 2.5mg Q2min x4 PRN</td>
<td>- 1mg + 0.5mg x2 &gt;60yrs or ill</td>
</tr>
<tr>
<td>- Fentanyl 75or 50 + 25mcg Q5-10 PRN max 200</td>
<td>- Dosing within 12 minutes</td>
</tr>
</tbody>
</table>

If any patient insufficiently sedated after protocol, then PRN Midaz given.
Endpoints
Adequate Sedation or Recovery

- Procedure started when MOAA/S score ≤ 4
- Fully Alert (recovered) = MOAA/S 5 x 3

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is called loudly and/or repeatedly</td>
</tr>
<tr>
<td>2</td>
<td>Responds only after mild prodding or shaking</td>
</tr>
<tr>
<td>1</td>
<td>Responds only after painful trapezius squeeze</td>
</tr>
<tr>
<td>0</td>
<td>No response after painful trapezius squeeze</td>
</tr>
</tbody>
</table>

Gastrointest Endosc 2018;88:427-37
Endpoints:

Timing

- Time to MOAA/S ≤3 (responds to loud calling of name)
  - Remimaz: 5.1 (±3.82) min
  - Midaz: 16.9 (±6.31) min
  - Placebo: 20.3 (±4.34) min

<table>
<thead>
<tr>
<th>TABLE 7. Mean times for recovery (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>From end of procedure to fully alert</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>7.35 (5.78)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>21.95 (17.74)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>15.84 (11.57)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>From procedure and until walking test passed</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>43.81 (13.26)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>54.50 (20.26)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>48.75 (14.44)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>From last study medication until walking test passed</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>50.94 (13.84)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>65.10 (18.77)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>58.07 (14.4)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>From start of medication to ready for discharge</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>60.34 (13.7)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>87.95 (21.07)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>77.27 (15.85)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>End of study medication to back to normal</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>330.71 (484.09)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>572.67 (626.75)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>553.11 (502.92)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>.001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Time to fully alert from last dose of IMP/rescue, min</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>14.36 (5.39)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>31.93 (16.81)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>25.19 (11.26)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Time to ready for discharge from end of procedure, min</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>42.65 (13.74)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>53.18 (20.55)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>47.92 (14.68)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Time to ready for discharge from last dose of IMP/rescue, min</td>
</tr>
<tr>
<td>Remimazolam</td>
</tr>
<tr>
<td>49.78 (14.33)</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>63.78 (19.09)</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>57.44 (14.56)</td>
</tr>
<tr>
<td>P value (remimazolam vs placebo)</td>
</tr>
<tr>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Endpoints:

COgnition

Remimazolam

• Better verbal learning recall scores with remimazolam v. midaz.

• Intraop Recall: similar rates for Remimazolam, midaz, placebo

Cognition

• Long term cognitive effects of benzo on elderly NOT examined
Endpoints
Hemodynamics and Respiration

- Remimazolam:
  - Less hypotension
- Remimazolam:
  - Less respiratory depression/hypoxia

### TABLE 9. Incidence of treatment-emergent adverse events

<table>
<thead>
<tr>
<th>System organ class and preferred term</th>
<th>Remimazolam</th>
<th>Placebo</th>
<th>Midazolam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 296</td>
<td>N = 60</td>
<td>N = 102</td>
<td>N = 458</td>
</tr>
<tr>
<td>Any treatment-emergent adverse events</td>
<td>218 (73.6%)</td>
<td>47 (78.3%)</td>
<td>93 (91.2%)</td>
<td>358 (78.2%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>184 (62.2%)</td>
<td>41 (68.3%)</td>
<td>83 (81.4%)</td>
<td>308 (67.2%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>115 (38.9%)</td>
<td>25 (41.7%)</td>
<td>63 (61.8%)</td>
<td>203 (44.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (19.9%)</td>
<td>17 (28.3%)</td>
<td>18 (17.6%)</td>
<td>94 (20.5%)</td>
</tr>
<tr>
<td>Diastolic hypertension</td>
<td>29 (9.8%)</td>
<td>6 (10.0%)</td>
<td>9 (8.8%)</td>
<td>44 (9.6%)</td>
</tr>
<tr>
<td>Diastolic hypotension</td>
<td>23 (7.8%)</td>
<td>4 (6.7%)</td>
<td>9 (8.8%)</td>
<td>36 (7.9%)</td>
</tr>
<tr>
<td>Systolic hypertension</td>
<td>16 (5.4%)</td>
<td>5 (8.3%)</td>
<td>6 (5.9%)</td>
<td>27 (5.9%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>53 (17.9%)</td>
<td>14 (23.3%)</td>
<td>26 (25.5%)</td>
<td>93 (20.3%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>33 (11.1%)</td>
<td>7 (11.7%)</td>
<td>16 (15.7%)</td>
<td>56 (12.2%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>23 (7.8%)</td>
<td>7 (11.7%)</td>
<td>13 (12.7%)</td>
<td>43 (9.4%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>11 (3.7%)</td>
<td>4 (6.7%)</td>
<td>6 (5.9%)</td>
<td>21 (4.6%)</td>
</tr>
<tr>
<td>Bradypnea</td>
<td>4 (1.4%)</td>
<td>2 (3.3%)</td>
<td>3 (2.9%)</td>
<td>9 (2.0%)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>3 (1.0%)</td>
<td>2 (3.3%)</td>
<td>1 (1.0%)</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
<td>2 (0.4%)</td>
</tr>
</tbody>
</table>

Gastrointest Endosc 2018;88:427-37
• Pts presenting for straight cardioversion (no TEE)
• Standard: propofol + Lidocaine
• Remimaz per package (initially)
• pilot from 6/21-11/21
• 67 Rochester pts
Survey

1) How many times have you administered remimazolam previously?
   □ Never □ Once □ Twice □ 3 or more

2) If you were not using remimazolam, which sedative would be your primary sedating agent used for this patient/procedure?
   □ Midazolam □ Propofol □ Other

3) Did you dose remimazolam using the ASA physical status classification?
   □ Yes □ No
   a. If yes, did this dosing guide result in adequate sedation/anxiolysis?
   □ Yes □ No
   b. If no, please explain: __________________________

4) Did you at any point feel your patient was over-sedated?
   □ Yes □ No

5) Did the patient have respiratory depression requiring intervention?
   □ Yes □ No
   a. If yes, describe intervention(s): __________________________

6) Did the patient experience an adverse event?
   □ Yes □ No
   a. If yes, please explain: __________________________

7) Rate your experience with remimazolam sedation compared to sedation with midazolam for procedural sedation.
   1 2 3 4 5
   Much worse Worse About the same Better Much better

8) Rate the recovery time from remimazolam compared to recovery time from midazolam.
   1 2 3 4 5
   Much slower Slower About the same Faster Much faster

9) Would you recommend expanded use of remimazolam to nurse-sedation practices?
   □ Yes □ No

10) Would you recommend expanded use of remimazolam to other anesthesia practices?
    □ Yes □ No

11) Please share any other feedback about the use of remimazolam below:

Remimazolam Procedural Sedation Pilot

Cath Lab (MB4)

Affix Patient Label Here

Mixing instructions:
1. Prepare a syringe of 0.9% sodium chloride with a volume of 8.2 mL
2. Mix with one 20 mg vial of remimazolam
3. Final concentration 2.5 mg/mL

Dosing guide:

<table>
<thead>
<tr>
<th>ASA PS Score</th>
<th>Initial Dose</th>
<th>Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>3-4</td>
<td>2.5 mg</td>
<td>1.25 mg</td>
</tr>
</tbody>
</table>

*Remimazolam is NOT compatible with Lactated Ringer’s*

*Flush the line with saline before and after administration.*

Questions:

If you have any questions about this pilot, please contact any of the following: George Gilkey, MD, Nathan Brinkman, PharmD, RPh, or Karen Nase, APRN, CRNA, DNP
SURVEY DATA AS OF 11/30/21
AGGREGATED AZ, FL, & RST

• Survey responses

Slide courtesy of Nate Brinkman PharmD
Respiratory Depression

survey data

• Chin lift/jaw thrust (10 patients)
• Mild apnea, resolved spontaneously
• Used ‘awake’ intubation
• Held mask over face; snoring
• Obstructed
• Reminded to breath
Adverse reactions

survey data

- Itching arm and eyes, redness
- Patient moving a lot
- Patient yelled “ouch that hurts” with cardioversion
  - NB: no recall!

Slide courtesy of Nate Brinkman PharmD
Survey Data
Aggregated AZ, FL, & RST

Sedation compared to midazolam

Survey responses

- Much worse: 1
- Worse: 9
- About the same: 66
- Better: 82
- Much better: 52

Slide courtesy of Nate Brinkman PharmD
Survey Data
Aggregated AZ, FL, & RST

Recovery time compared to midazolam

Survey responses

<table>
<thead>
<tr>
<th>Recovery Response</th>
<th>Survey Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much slower</td>
<td>0</td>
</tr>
<tr>
<td>Slower</td>
<td>7</td>
</tr>
<tr>
<td>About the same</td>
<td>28</td>
</tr>
<tr>
<td>Faster</td>
<td>73</td>
</tr>
<tr>
<td>Much faster</td>
<td>100</td>
</tr>
</tbody>
</table>

Slide courtesy of Nate Brinkman PharmD
Cardioversion

What did we learn?

• Package dosing- too low. 8-12mg more realistic
• Slower onset than propofol- be patient
• Don’t expect it to be propofol
• Pts wake up quickly: 10min or less
• Reconstitute in 10ml = 2mg/mL
• Minimal respiratory depression
• Hemodynamic stability
Use at Mayo Clinic
Enterprise data (as of 1/25/22)

- 434 patients have been treated with Remimazolam
  - Rochester: 166
  - Florida: 191
  - Arizona: 64

- Mean dose 3.6mg Median dose 2.5mg
- 1634 total doses administered
Other uses at Mayo Clinic

- Awake Fiberoptic intubation
- TEE
- Trans-carotid TAVR
- Awake Craniotomy (Jacksonville)
- G-tube placement (Jacksonville)
- GI cases (Jacksonville)
Off Label Use:

- Infusion for general anesthesia
  - Induction:
    - 12mg/kg/hr
    - 6mg/kg/hr (15-20s slower)
  - Maintenance:
    - 1-3mg/kg/hr

Lohmer et al. The Journal of Clinical Pharmacology 2020, 60(4) 505–514
Off Label:
Infusion Offset

Women: 0.5mg/kg/hr + BIS 60

Men: 1.5mg/kg/hr + BIS 60

Lohmer et al. The Journal of Clinical Pharmacology 2020, 60(4) 505–514
Off Label use:

Time to emergence

- By 30 minutes: 20% probability of not being extubatable
Remimazolam Arm
- Induction 12mg/kg/hr Remimazolam
- Maintenance:
  - Rmz: 1mg/kg/hr
  - Remifent: 0.1mcg/kg/hr

Propofol Arm
- Propofol infusion
  - Remifent 0.1mcg/kg/hr
NeuroSurgery
Awake Craniotomy – Sato et al.

• LMA- iGel
• Leviteracetam + Dexamethasone
• 8/15 RMZ pt’s got flumazenil
• Remimazolam wakeup time: 14.8±2.6 minutes
• Propofol wakeup: 19 ±33 minutes
• More nausea with Remimazolam
Neurosurgery with SSEP and VEP. N=9

Remimazolam 0.8mg/kg/hr + Remifentanil 0.2-0.4mcg/kg/hr v. propofol

VEP:
  • Amplitude: greater with RMZ v. propofol
  • Latency: no difference

SSEP: no significant difference RMZ v. Propofol for latency or amplitude
Neuro Surgery
Motor Evoked Potentials – Arashiro et al

• N=1

• Pt with Alström syndrome
  • Dilated Cardiomyopathy, DM, HLD, obesity, scoliosis

• Spinal Fusion
  • Remifentanil 0.3mcg/kg/min
  • Remimazolam 0.5-1.0 mg/kg/hr
  • No changes in MEPs
Rare disease populations:

- Myotonic dystrophy- Remimaz + Remifent
- Duchenne Muscular Dystrophy- Remimaz + remifent
- Extreme benzo tolerance- Remimaz infusion
Patient Subsets:

The unknowns:

• Pediatrics – no published studies on pediatric patients
• Obstetrics: unknown placental transfer
• Lactating Women- no published data on presence of remimazolam in breast milk or nursing infant
Conclusions:
Where do we go?

Availability

• Soon to be available in Anesthesia workroom pyxis
• Not yet available as infusion
Conclusions:
Where do we go?

• Pros and Cons: Context dependent
• Con: $40/vial
• Very titratable
• Reversible
• Quick wakeup with minimal grogginess

• Good hemodynamic profile
• Minimal respiratory depression when used as solo agent
QUESTIONS & ANSWERS

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