Use of Flumazenil to Reverse Treatment Associated Delirium

J.J. Rasimas, M.D., Ph.D.
Associate Professor
Psychiatry and Emergency Medicine
PinnacleHealth Toxicology Center
Penn State University College of Medicine
NIH Staff Clinician
NIMH Experimental Therapeutics and Pathophysiology Branch

Disclosure: J.J. Rasimas, M.D., Ph.D.

With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or spouse/partner) and any for-profit company in the past 24 months which could be considered a conflict of interest.
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The views presented herein are my own and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

Background

- Delirium
  - Syndrome of global brain dysfunction
  - Phenomenology varies
  - Medical etiology
  - 10-30% of hospital inpatients (and ED elderly)
  - Increased mortality risk
  - Frequently exacerbated by Rx
- Ethanol Withdrawal
  - Delirium may accompany the syndrome
  - May just as easily accompany the treatment

Case

- 68 M h/o back pain, EtOH dependence, insomnia
  - Takes amlodipine, carisoprodol, trazodone
  - s/p MI and urgent cardiac procedure
  - Developed withdrawal beginning 24 h post admission
  - Treated with scheduled BZDs and requires 1:1
  - Nights worse, PRN zolpidem.
  - Concerns about cognition...
    - BZDs stopped during the day on day #7
    - No better...
Consultation

 › Consult for confusion, Hospital day #8
   › Vitals: T 37.2, HR 77, RR 16, BP 122/72, O2 Sat 96% 2L
   › Poor attention, intermittent frustrated upset
   › Slow, poorly coordinated motor function
   › No focal neurologic findings, mild symm. hyporeflexia
   › Lungs clear (diminished at bases), otherwise benign
   › Skin warm, mildly moist, intact
   › Foley in, leg out, mitts on...wits gone

 › Diagnosis: Delirium

Routine

 › There’s a standard response
   › Withdrawal likely resolved at this point...
   › D/C BZDs, perhaps with a short taper
   › Attend to electrolyte imbalances, respiratory status
   › Though unlikely, consider sites of potential infection
   › Maintain day/night routines & appropriate stimulation
   › Haloperidol for serious agitation/confusion
   › Or...
     › Flumazenil 0.5 mg IV over 30 sec into running IV
     › In 1 minute, cognition clears with calm
     › Patient responds to orientation and reassuring information about his medical condition

Flumazenil

• Competitive antagonist at the benzodiazepine receptor binding site
• Inverse agonist activity
• Agonist at high doses?

• Indications
  › Extubate / avoid intubation in toxic sedation threatening airway loss
  › Reverse respiratory depression
  › Diagnostic aid in coma
So Let's Cut to the Chase...

FLUMAZENIL IN ALCOHOL WITHDRAWAL: A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY
JOHN POTOKAR*, NICK COUPLAND, PAUL GLUE, SIMON GROVES, ANDREA MALIZIA, JAYNE BAILEY, SUE WILSON and DAVID NUTT

Psychopharmacology Unit, School of Medical Sciences, University Walk, Bristol BS8 1TD, UK
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Abstract - The purpose of the present study was to study \( \gamma \)-aminobutyric acid (GABA)-A receptor function in alcohol-dependent subjects during withdrawal, using the benzodiazepine antagonist flumazenil. In particular, we wanted to examine the hypotheses that an endogenous inverse agonist ligand at the GABA-A benzodiazepine receptor (\( \text{GABA}_\text{R} \)) is active during withdrawal (in which case flumazenil should be anxiolytic), or whether chronic alcohol intake results in a shift in sensitivity of the receptor in the inverse agonist direction (in which case flumazenil should be anxiogenic).

Results from 15 alcohol-dependent subjects in a double-blind placebo-controlled cross-over study showed that flumazenil was neither anxiolytic nor anxiogenic, although withdrawal scores were reduced during the course of the study. The fact that flumazenil was not anxiogenic, as it is in panic disorder, suggests that the \( \text{GABA}_\text{R} \) is functioning differently in these two clinically similar conditions.

Study
- 15 EtOH dependent patients
  - All gave written informed consent
  - (So, not our patients...)
  - Excluded h/o seizures, DTs, EtOH detected
- CIWA scores, mean baseline 15.6
  - End of study (2 hours) 8.6 (\( p = .002 \) )
- Flumazenil 2 mg over 1 minute
- Double-blind placebo crossover
  - No effect on HR, BP, anxiety (main outcome)
  - No seizures
Reality

- The primary goal is often safety in severe cases
- Sedation must be tolerated
- So...
  - Diazepam 10-20 mg IV q5min until effective
  - Increase dose to 40, 60, 80, 100, 120, 150, 200 mg at a time
- Typically maintain with PRN lorazepam q1h, dosed to mental status (“Riker 3”)
- But it’s an imperfect art and science, and errors are often corrected in our clinical practice with flumazenil

PinnacleHealth Study

- Prospective gathering of all case data from July 2009 to July 2010
  - Electronic searches for antidote Rx
  - Demographics and diagnoses
  - Corroborated with electronic and written medical records (JIR, KS, and JWD)

Clinical Use

- Patient Selection: Sedation or confusion with relaxed markers of neural and autonomic status
- Monitoring: Physical exam / Standard
  - Cardiac monitoring
- Dose: 0.5 mg IV over 30 sec
  - Into a running IVF line
  - Consider 0.2 mg in cases of equivocal exam
- Treatment:
  - If no response in 2 min, abandon
  - If effective, repeat dose q1 hour PRN
  - Consider increase to 1 mg if effect wanes before 1 hour
Antidote Treatment 2009-2010

<table>
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<th>Total</th>
<th>Response</th>
<th>Adverse</th>
<th>Men</th>
<th>Response</th>
<th>Women</th>
<th>Response</th>
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<tbody>
<tr>
<td>Ages 3-9</td>
<td>122</td>
<td>108</td>
<td>79</td>
<td>16</td>
<td>125</td>
<td>196</td>
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<tr>
<td>Mean 42</td>
<td>80%</td>
<td>6%</td>
<td>76%</td>
<td>82%</td>
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Adverse Events 2009-2010

- Flumazenil
  - 3 drooling, 7 anxiety, 2 self-stimulation episodes (1 patient)
- Sexual acting out: 40M, Spina bifida, baclofen & pregabalin toxic
- Anxiety with arousal most common, respond to empathic presence
- Drooling never produced adverse consequences
- No Seizures

Comorbidities and Antidote Rx '09-'10

<table>
<thead>
<tr>
<th>Total</th>
<th>Flumazen</th>
<th>Response</th>
<th>Adverse</th>
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<tbody>
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<td>Heart Disease</td>
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<td>12</td>
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<tr>
<td>Lung Disease</td>
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<td>12</td>
<td>10</td>
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<tr>
<td>Seizure Disorder</td>
<td>10</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Chronic BZDs</td>
<td>10</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Sedative Abuse</td>
<td>10</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Heart and Lung disease predicted better than average response to flumazenil
Seizure disorder predicted lower likelihood of response to flumazenil
Chronic use of BZDs correlated with greater likelihood of anxiety upon awakening
Markers of Risk:
- Sedative toxicity
  - 147 cases – 129 received flumazenil
  - 11 of the 12 minor adverse events
- Ethanol toxicity
  - 112 cases – 20 received flumazenil
  - 2 of the 12 minor adverse events
- Antiepileptic Drug Toxicity
  - 77 cases – 41 received flumazenil
  - 1 of the minor adverse events
  - Lower rate of positive response (38%)

When We Overshoot
- EtOH withdrawal
  - 53 cases – 17 received flumazenil
  - 85% response rate, 1 case of anxiety
- Sedative withdrawal
  - 6 cases – 2 received flumazenil
  - Both responded
  - No adverse effects
- Opioid withdrawal
  - 9 cases – 1 received flumazenil

Focused Study – Dr. Moore
- Retrospective study from December 2006 to June 2012 of EtOH withdrawal patients
  - Electronic searches for BZD and antidote Rx
  - Demographics and diagnoses
  - Estimated last EtOH consumption
- 85 Patients
  - 25 with documented history of seizures
  - 62 oversedate, 54 intermittently agitated (41 both)
  - Flumazenil given 4.7 days post abstinence (avg.)
Results

- 78.8% positive response rate
  - Similar to overall response rate with flumazenil
  - Clinical results
    - Participation in care, feeding, PT, and foley removal
- Over 80% required repeat dosing (avg 5.6)
- 2.4% negative response rate
  - Increased agitation
  - No major adverse events
  - No seizures

Response after administration of FMZ 0.5 mg (N=71)

Response after administration of FMZ 0.2 to 0.3 mg (N=14)
Limitations

- Retrospective data mining
- Incomplete medical records
  - Emergency department medications
  - Minor adverse effects
- Subjective assessments
  - Recorder Bias
- Not every dose of antidote directly observed
- No comparison groups

Conclusions

- Oversedation is a common problem after treatment of severe withdrawal
- Flumazenil is safe and effective for confusion / sedation / coma suspected secondary to sedatives
  - Recovery from withdrawal treatment
  - BZD induced delirium
  - Reversal of (un)-intended sedation
- Safe, despite worry, in patients who appear to be at risk:
  - Chronic BZD users, underlying seizure disorders...
  - At the end of EtOH withdrawal Rx
- Safe and effective when the clinical presentation is consistent with its use

Clinical Use

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- Dose: 0.5 mg IV over 30 sec
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- Treatment:
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  - Consider increase to 1 mg if effect wanes before 1 hour
Hepatic encephalopathy

- Pathophysiology suggests presence of compounds with BZD-like activity
- Phenomenology of the condition is consistent with this hypothesis
- Case reports and series suggest utility
- Same dose 0.5 mg to start, consider increase
- Expect diminishing returns...

References

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