Short of breath, short of evidence – but does intranasal midazolam help?

J. Hardy, C. Randall, A. Tapuni, E. Pinkerton, K. Gibbons, S. Allan
Intranasal midazolam for the palliation of dyspnoea in patients with life-limiting disease
Background

• Dyspnoea/ anxiety interaction
• Largely negative studies of benzodiazepines in dyspnoea, anxiety component not well articulated
• Need for patient tool that allows greater autonomy for dyspnoea control
• Excellent prospective audit results of MNS in dyspnoea 2008 from Arohanui Hospice- Proc. HNZ
Dyspnoea - Midazolam Nasal Spray vs Placebo

• Hypothesis:

Intranasal midazolam is superior to placebo for the palliation of dyspnoea in patients with optimally treated life limiting disease
Study Design

• Randomised, double blind, cross over study
• Malignant or non malignant life limiting disease under Palliative Care Services
• Multi-centre: Mater Health Services, Brisbane; Arohanui Hospice, Palmerston North, Mercy Hospice, Auckland; Mary Potter Hospice, Wellington
• HREC, Australia and NZ National Ethics committee approval 2009
Inclusion Criteria

• 18 years plus
• Life limiting disease
• English speaking or interpreter
• Patients with an average dyspnoea ≥3 (0-10 rating where 10 is worst possible breathlessness)
• Karnofsky PS >30
• Competent to operate nasal spray and diary events
• Stable medication within 48 h of commencing, as regards dyspnoea
Exclusions

- Resolving respiratory condition
- Concurrent unstable benzodiazepine therapy
- Unstable opioid use 48h before starting trial
- ≥3 doses of opioid b’through/day
- Adverse reaction to benzodiazepine
- Respiratory depression <10 breaths/min
- Narrow angle glaucoma, myasthenia gravis
- Alcohol/ drug dependency
- Therapeutic interventions for dyspnoea while on trial
- Any change in oxygen prescription during trial
Study Medication

- Midazolam hydrochloride inj 15mg/3ml, 2 amps in metered dose spray 0.5 mg/spray
- Placebo - citric acid 7.65mg/ml in same spray device, pH similar “feel” to midazolam
- 6 identical spray bottles for 6 days of use 1-6 with equal midazolam or placebo bottles
- Total 3 inhalations, alternate nostrils (1.5 mg midazolam) q4hrly prn
Randomisation

• All possible combinations of SNS included
• Individual patient SNS allocation 1-6
  responsibility of local pharmacist
• Double blind nature maintained
• Rescue medication was oral opioid - generally morphine elixir
Study Procedure

- Patients screened, eligibility, consented
- Given instructions, 6 labelled study nasal sprays (SNS)
- Asked to use a SNS as their first rescue dose for dyspnoea using bottle 1 on the first day, bottle 2 on the second day etc
- If no dyspnoea they did not have to use a spray
- All bottles had to be used within 14 days
- First dose each day was formally assessed. At end of each day, patients recorded how many times they used SNS and any benefits
- Assessed clinically at baseline, 7 days and 14 days
- Phone contact day 3 and day 10
Assessment tools used

- Modified dyspnoea assessment scale
- Hospital Anxiety and Depression Scale HAD-pt
- Cancer dyspnoea scale-pt
- Covi anxiety scale- 3 point observer tool
- Karnofsky performance scale
- Dose cards, daily diary, toxicity recording
- Recent CBC, concomitant drugs, prn, O2
Patients assessed at:

- Baseline
- Day 3 - telephone
- Day 7
- Day 10 telephone
- Day 14
- Patient enrolment anticipated- 200 over 3 years
- First pt 13/10/09, final pt 27/12/12
End points

• Primary end point was dyspnoea intensity score at 15 mins compared to baseline

• Secondary endpoints were difference in dyspnoea scores from baseline at 5, 30 and 60 mins, drowsiness and anxiety

• A difference in dyspnoea intensity score from baseline at 15 mins of ≥ 2/10 was defined as a positive outcome
Results

• 76 patients recruited
• 62 available for analysis
• No differences in any parameters between Australia vs NZ, so data combined
• Cancer 50, Heart 4, Respiratory 20, N/A 2
• Number of available bottles available at each time point:
## SNS Results

<table>
<thead>
<tr>
<th>Time point</th>
<th>Total 250 SNS available</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td>5 min</td>
<td>248</td>
<td>99.2</td>
</tr>
<tr>
<td>15 min</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td>30 min</td>
<td>241</td>
<td>96.7</td>
</tr>
<tr>
<td>60 min</td>
<td>234</td>
<td>93.6</td>
</tr>
</tbody>
</table>
Results

• **No** significant differences are seen between bottles A and B at *any* time point throughout the study in:
  
  • Change score overall **or**
  
  • Successful change between bottles A or B
Results- correlated with anxiety

• In a correlation of HAD score and change/successful change a significant difference was shown at 30 minutes

<table>
<thead>
<tr>
<th>Time point</th>
<th>n</th>
<th>coef</th>
<th>95%CI</th>
<th>p</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>208</td>
<td>-.11</td>
<td>0.54</td>
<td>.81</td>
<td>0.611</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>208</td>
<td>-.34</td>
<td>0.071</td>
<td>.75</td>
<td>0.478</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>202</td>
<td>-.34</td>
<td>0.122</td>
<td>.51</td>
<td>.26, 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>198</td>
<td>0.04</td>
<td>0.876</td>
<td>.85</td>
<td>0.657</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Toxicity - NCI score

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>D3 score</th>
<th>D7 score</th>
<th>D14 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nasal reaction</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lacrimal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

1 withdrawal for nasal/tear (3/5 intensity), all other relatively low grade scores.
Discussion

• Midazolam nasal sprays have become commonly used in many palliative care services

• Unfortunately this double blind intrapatient crossover study failed to demonstrate any meaningful benefit with respect to dyspnoea or anxiety for midazolam when compared to placebo
Conclusions

• This study is underpowered to confirm or deny the hypothesis
• However no significant difference is seen between bottles A and B
• Intra-participant to inter-participant
• Sub group analysis may indicate a useful area of exploration, namely those patients with breathlessness who are anxious
Conclusions

• Missing data & funding
• A strength of the study was in the design that conformed to the guidelines of the National Cancer Research Institute Palliative Care Breathlessness Subgroup. This standard approach should facilitate comparison with other studies
• Cochrane analysis has not demonstrated a useful role for benzodiazepines in SOB studies to date
• Opioids remain the palliative medication of choice for dyspnoea
Next Steps

• Has this research effected a change in practice?
• Questionnaire being developed
• Survey GPs, pharmacists regarding any change in practice as a result of this research
• Closing the loop
• Further research??
Our thanks

• **Contributing centres:** Mary Potter Hospice, Wellington; Mercy Hospice, Auckland; Mater PC Service, Brisbane; Arohanui Hospice, Palmerston North- and all our patients!

• **Funders:** Palmerston North Medical Research Foundation, JP Kelly Fund (Mater Health), Cancer Society of NZ Central Districts Division Inc, Arohanui Hospice Service Trust.