Respiratory depression related to buprenorphine and diazepam combination in rats: study of the pharmacodynamic mechanism of interaction

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Buprenorphine (BUP):
- Partial agonist of µ opioid receptors and antagonist of κ opioid receptors
- Ceiling respiratory effects at elevated doses

Dahan A. Br J Anesthesiol 2005

INTRODUCTION
«Ceiling effect»
- Difficulty in cases analyses
- Misuse of BUP (IV injection of crushed tablets)
- Co-ingestion of benzodiazepines (BZD)

Pirnay S. Addiction 2004

Problem: BUP-related asphyxica deaths
- Difficulty in cases analyses
- Misuse of BUP (IV injection of crushed tablets)
- Co-ingestion of benzodiazepines (BZD)

Kenta F. Forensic Sci Int 2002

Experimental data (1): BUP and BZD alone

Diazepam (DZP) 20 mg/kg SC
BUP 30-120 mg/kg IV

Gueye P. Tox Sci 2001

Absence of significant respiratory depression using blood gas analyses, when administered alone

Experimental data (2): BUP+BZD combination

Midazolam 160 mg/kg IP
BUP 30 mg/kg IV

Gueye P. Tox Sci 2002

Mechanisms of interaction BZD / BUP
- Pharmacokinetics PK
- Cerebral distribution of BUP
- Hepatic metabolism (CYP)
- Pharmacodynamics PD
- Interaction at the command level of breathing
- Increases in peripheral & central effects
OBJECTIVES

1- Assessment of respiratory effects of DZP / BUP combination

2- Investigation of the pharmacodynamic mechanism of DZP / BUP interaction using specific antagonists of the involved receptors

Experimental model

- Sprague Dawley Rat
- 8-12 weeks
- 250-350 g

The protocol was approved by the ethical committee of Paris Descartes-University (n° P2.BM.128.10)

Materials and Methods

Drugs and antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Details</th>
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<tbody>
<tr>
<td>Diazepam</td>
<td>20 mg/kg SC</td>
</tr>
<tr>
<td>Suprasol</td>
<td>10 mg/kg IP</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>5 mg/kg IP</td>
</tr>
<tr>
<td>Naloxone</td>
<td>10 mg/kg SC</td>
</tr>
<tr>
<td>Nalorphine</td>
<td>10 mg/kg SC</td>
</tr>
</tbody>
</table>

Euthanasia at the end of experiment

BLOOD SAMPLING

Clinical parameters

- Rectal temperature
- Consciousness
- Tonus
- Walk

Respiratory parameters

- Inspiratory time (T1)
- Expiratory time (T2)
- Tidal volume (Vt)
- Respiratory frequency (f)
- Minute ventilation (V’E)

Plethysmography (1)

7-10 days before device calibration

Plethysmography (2)

Leaking test

Repeatability

<table>
<thead>
<tr>
<th></th>
<th>0 s</th>
<th>20 s</th>
<th>40 s</th>
<th>60 s</th>
<th>80 s</th>
<th>100 s</th>
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<tr>
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<td>2.06</td>
<td>2.08</td>
<td>2.15</td>
<td>2.01</td>
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Reproducibility

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</table>
**EXPERIMENTAL PROTOCOL**

**Study n°1**

- Description of respiratory effects using arterial blood gases and plethysmography
- Randomization: n=8 per group

**EXPERIMENTAL SCHEMA**

**Study n°2**

- Investigation of the pharmacodynamic mechanisms of interaction
- Using arterial blood gases and plethysmography
- Randomization: n=6 per group

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**Statistical analysis**

- For each parameter:
  - Evolution time by time over 240 min
  - Area under the curve (AUC) over 60 min
- Results were expressed as Mean +/- SEM.
- Study of the difference between treatments:
  - > 2 groups: Analysis of variance of one or two factors followed by multiple comparisons with post-tests and Bonferroni correction
  - 2 groups: Mann-Whitney tests
- Prism 5.0 software (GraphPad Software)

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**RESULTS Study 1**

= Respiratory depression

- Parameter
- \( V_{M} = \)

\[ \frac{1}{f} = T_I + T_E \]

**RESULTS Study 2**

= Effects of antagonists on respiratory depression

- GABA Antagonists
- Opiates Antagonists

- Blood gas analyses
- Plethysmography
DISCUSSION (1)

DZP/BUP = Respiratory depression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DZP</th>
<th>BUP</th>
<th>DZP/BUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_m )</td>
<td>↑↑↑</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>( \text{PaCO}_2 )</td>
<td>↓</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>( V_T )</td>
<td>→</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>( f )</td>
<td>↑</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>( T_{II} )</td>
<td>→</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>( T_E )</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

DISCUSSION (2)

reversibility by FLZ and NLZ

<table>
<thead>
<tr>
<th>Co-ingestion</th>
<th>FLZ/DZP/BUP</th>
<th>NLZ/DZP/BUP</th>
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<tbody>
<tr>
<td>73%</td>
<td>95%</td>
<td>89%</td>
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<tr>
<td>0.04</td>
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<table>
<thead>
<tr>
<th>( \text{PaCO}_2 )</th>
<th>[45-55]</th>
<th>[45-56]</th>
<th>[36-57]</th>
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<tbody>
<tr>
<td>51</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>NALOXONE</th>
<th>81%</th>
<th>0%</th>
<th>71%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLUMAZENIL</td>
<td>0%</td>
<td>87%</td>
<td>60%</td>
</tr>
<tr>
<td>0.0001</td>
<td></td>
<td></td>
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</tbody>
</table>

DISCUSSION (3)

mechanisms of interaction: addition of peripheral and central effects?

BZD

- Decrease of \( V_T \) compensated by an increase in \( f \)
- Increase of \( T_{II} \) without modification of \( f \)

BUP

- Decrease of \( V_T \) without modification of \( f \)
- Increase of \( T_{II} \) without modification of \( f \)

HYPOTHESIS: upper airway obstruction = PERIPHERAL

RESPIRATORY DEPRESSION = CENTRAL

DISCUSSION (4)

mechanisms of interaction: interaction between GABA-A and \( \mu \) receptors

- Presence: in the same structures in CNS
- Implication in the control of respiration
- Interaction mediated by G protein linked to opioid or GABA receptors

Kalyuzhny A. Neuroreport 2000
Yamasaki K. Brain res 1982
Agnati B. Pharmacol Rev 2003

BZD: the BUP-induced down regulation of \( \mu \) receptors

Van Domp E. Anesthesiology 2006
• DZP/BUP = RESPIRATORY DEPRESSION
• Mechanisms:
  - Reduction in V₁ (DZP) and increase in V₂ (BUP)
  - Addition of peripheral and central effects?
  - Implication of GABA-A and μ receptors
  - Interaction of GABA A and μ receptors?

CONCLUSION

Thank you for your attention