Buccal naloxone

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Declarations RM

• RM has undertaken an unpaid student industry placement with Mundipharma Research Ltd., with focus on the analysis of naloxone nasal spray formulations.

• King’s College London has separately applied to register intellectual property on a novel buccal naloxone formulation with which JS and RM are involved.

• RM is a consultant for the United Nations (UNODC), supporting a naloxone study in Central Asia.
Declarations JS (personal & institutional)

- NHS provider (community & in-patient); also Phoenix House, Lifeline, Clouds House, KCA (Kent Council on Addictions).
- Dept of Health, NTA, Home Office, NACD, EMCDDA, WHO, UNODC, NIDA.
- Dialogue and work with pharmaceutical companies re actual or potential development of new medicines for use in the addiction treatment field (incl re naloxone products), including (past 3 years) Martindale, Indivior, MundiPharma, Braeburn and trial product supply from iGen.
- SSA (Society for the Study of Addiction); UKDPC (UK Drug Policy Commission), and two Masters degrees (taught MSc and IPAS) and an Addictions MOOC.
- Work also with several charities (and received support) including Action on Addiction, and also with J Paul Getty Charitable Trust (JPGT) and Pilgrim Trust.
- The university (King’s College London) has registered intellectual property on a buccal naloxone formulation, and JS has been named in a patent registration by a Pharma company as inventor of a novel concentrated naloxone nasal spray.
Nasal naloxone: What have we solved?

The formulation:

- Nasal spray volume
- Max injectable concentration – 1mg/ml
- Best guess PK – 30-50% ??
- Vertical/horizontal

Max. dose through 2 nostrils – 0.2mg naloxone (old school)
1 | Nasal naloxone: What’s still a worry?

The route in practice:

- Nasal membrane abuse and damage
- Vomitus and secretions
- Bar set high – highly effective and easy IM (and low-cost)
2 | Injection-free alternatives: Buccal
Buccal and oral bioavailability of naloxone and naltrexone in rats

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Summary

The opioid antagonists naloxone and naltrexone are both known to undergo extensive first-pass metabolism after oral dosing. The buccal route was investigated as a potential alternative to oral administration. Oral and buccal bioavailabilities of naloxone and naltrexone were determined in rats. Less than 1% of oral naloxone or naltrexone was bioavailable, but buccal administration resulted in approximately 70% bioavailability for each drug.
2 | Other buccal products: Emergency midazolam

- Recent development for interim treatment of status epilepticus
- Similarly for emergency administration while awaiting ambulance
- Buccal route deemed suitable for family administration
2 | The possibility of buccal naloxone

The specification:

• Speed and reliability of effect
• Stable over time and extremes of temperature
• Easy to carry
• Good acceptability
• Low price for mass pre-provision
3 | Collaboration partners

Prof David Taylor
Psychopharmacology CAG; and Pharmacy, SLaM

Prof John Strang¹ & Rebecca McDonald
Addictions Department, IoPPN ¹ and Addictions CAG

Prof Peter Goadsby and colleagues
Clinical Research Facility (CRF)
King’s College Hospital | Denmark Hill

Drs Ben Forbes & Paul Royall
Drug Delivery Group
Institute of Pharmaceutical Science | Waterloo

Pharmacy Manufacturing Unit | Guy’s

Prof Bob Flanagan
Toxicology Unit
King’s College Hospital
3 | Instant-dissolving tablet: Development

**Stock solution**
Naloxone and pharmaceutical grade excipients in water for injection

**Solution**
Solution pipetted into blister wells (top) and frozen (bottom) ready for lyophilisation

**Ice**
Water vapour

**Temperature / Pressure**

**Frozen tablets**
Lyophilised using tailored temperature and pressure cycle

**Instant-dissolving tablet**
3 | Instant-dissolving tablet: Prototype

Naloxone 0.8 mg instant dissolving tablet
White porous tablet (17 mg, 10 x 20 mm)
4 | In vitro testing: Stability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
<th>0 months</th>
<th>9 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4°C</td>
<td>25°C</td>
</tr>
<tr>
<td>Tablet weight (mg)</td>
<td>16.9 - 20.7</td>
<td>17.8 ± 0.5</td>
<td>17.8 ± 0.5</td>
<td>17.6 ± 0.5</td>
</tr>
<tr>
<td>Dimension - length (mm)</td>
<td>20.0 - 30.0</td>
<td>29.4 ± 0.2</td>
<td>29.1 ± 0.3</td>
<td>29.1 ± 0.7</td>
</tr>
<tr>
<td>Dimension - width (mm)</td>
<td>14.0 - 18.0</td>
<td>16.1 ± 0.5</td>
<td>16.1 ± 0.3</td>
<td>16.0 ± 0.3</td>
</tr>
<tr>
<td>Disintegration test (s)</td>
<td>≤180</td>
<td>14.0 ± 5.9</td>
<td>9.0 ± 5.0</td>
<td>10.0 ± 5.0</td>
</tr>
<tr>
<td>Naloxone HCl assay (mg)</td>
<td>0.76 - 0.84</td>
<td>0.80 ± 0.01</td>
<td>0.81 ± 0.02</td>
<td>0.80 ± 0.03</td>
</tr>
</tbody>
</table>

- The tablets conformed reproducibly to quality specifications
- Chemical and physical stability over 9-months’ storage (25°C), with target drug content of 0.8 mg of naloxone HCl/tablet (HPLC assay)

4 | In vitro testing: Digital imaging dissolution assay

- Under all conditions, tablets dissolved fully (>90%) within 30 seconds (variation of: temperature, volume of fluid, dissolution medium)

4 | In vitro testing: Digital imaging dissolution assay

Figure 5. Effect of (A) temperature [volume 0.7 mL; medium – phosphate buffered saline], (B) fluid volume [temperature 35°C; medium – phosphate buffered saline], (C) dissolution medium [temperature 35°C; volume 0.7 mL] on the dissolution of the instant dissolving tablet using a digital image dissolution assay. Data represent mean ± SE, n=3.

5 | Buccal naloxone: Summary

• Advantage over solution: tablets greater stability?

• Ease of transport

• Addition of absorption enhancers possible

• Next steps: in vivo testing – human volunteer PK study
Thank you