The pharmacokinetics of IntraNasal DROPeridol in healthy volunteers (INKDROP Study)

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BACKGROUND

Droperidol is a butyrophenone antipsychotic agent that is used parenterally to treat nausea and vomiting, migraine and acute behavioral disturbance.

In the past few years, droperidol has regained popularity as a parenteral agent for treatment of acute behavioural disturbance in many Australian Emergency Departments.

Its rapid onset of action after parenteral administration make it ideal for use in the Emergency Department.

Intranasal use is not reported for droperidol.

Intranasal drug administration reduces need for intravenous cannula placement and risk of needle-stick injury, especially in patients with poor venous access.

The intranasal route has been used to administer various drugs with utility in the acute care (pre-hospital and Emergency Department) setting.

These include naloxone, fentanyl, ketamine, and ketorolac.

In addition, Miller et al (2008) showed that haloperidol had a bioavailability of 63% after intranasal delivery in a volunteer pharmacokinetic study.

We hypothesized that droperidol will be well absorbed intranasally.

METHOD

This was an open-label cross-over volunteer study comparing the pharmacokinetics of a single dose of intravenous (IV) and intranasal (IN) droperidol.

Seven male volunteers (50-100kg) received 0.02mg/kg of droperidol (5mg/mL, DORM, Phebra, Australia, 5mg/mL) by each route with a one-week washout period.

RESULTS

Seven male volunteers participated in the study:

- median age 23 yrs (range: 20 - 43),
- median weight 73 kg (range: 65 – 98),
- median height 180 cm (range: 170 – 195).

All patients had normal a 12-lead ECG pre-study and during droperidol administration. There were no cases of QT prolongation.

Table 1: Summary of Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Route of administration</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Intravenous (n=7)</td>
<td>Intranasal (n=7)</td>
</tr>
<tr>
<td>Tmax (hrs) (median +/- range)</td>
<td>0.25 (0.24-0.28)</td>
<td>0.5 (0.5-1.0)</td>
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<tr>
<td>Half-life (hrs) (mean +/- 95% CI)</td>
<td>2.02 (1.92-2.12)</td>
<td>2.37 (2.05-2.52)</td>
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<tr>
<td>Bioavailability (%)</td>
<td>100%</td>
<td>40%</td>
</tr>
<tr>
<td>Cmax (ng/mL) (median +/- range)</td>
<td>26.6 (14.5-86)</td>
<td>6.5 (2.6-8.0)</td>
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<tr>
<td>AUC to 10 hours (ng.hr/mL) (mean +/- 95% CI)</td>
<td>40 (33.7-62.2)</td>
<td>19 (11.5-26.6)</td>
</tr>
<tr>
<td>AUC to infinity (ng.hr/mL) (mean +/- 95% CI)</td>
<td>41.4 (35-64)</td>
<td>19.2 (12.3-28)</td>
</tr>
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</table>

* Unpaired t-test with Welch correction. + Mann-Whitney test

CONCLUSION

Intranasal delivery of droperidol resulted in a relatively low bioavailability of 40% compared to the intravenous route.

Time to peak concentration was delayed with intranasal administration (30 minutes for IN vs 15 minutes for IV).

However, all subjects reported some degree of sedation following both routes of administration.

The low bioavailability may be partially explained by our attempt to standardize administration volume in all subjects.

Using a higher dose with undiluted droperidol should result in greater absorption and bioavailability.

For example, 5mg of undiluted DORM® in 1ml volume (0.5mL to each nare).

The intranasal route of administration for droperidol may be useful for treatment of nausea/vomiting or migraine when intravenous access is impractical or may be delayed.

The intranasal route is likely to be impractical in situations where intravenous administration is impractical or may be delayed.

Clinical studies are needed to determine dosing thresholds and effectiveness of droperidol by the intranasal route.