A concentrated naloxone nasal spray for opioid overdose reversal: A pharmacokinetic study in healthy volunteers

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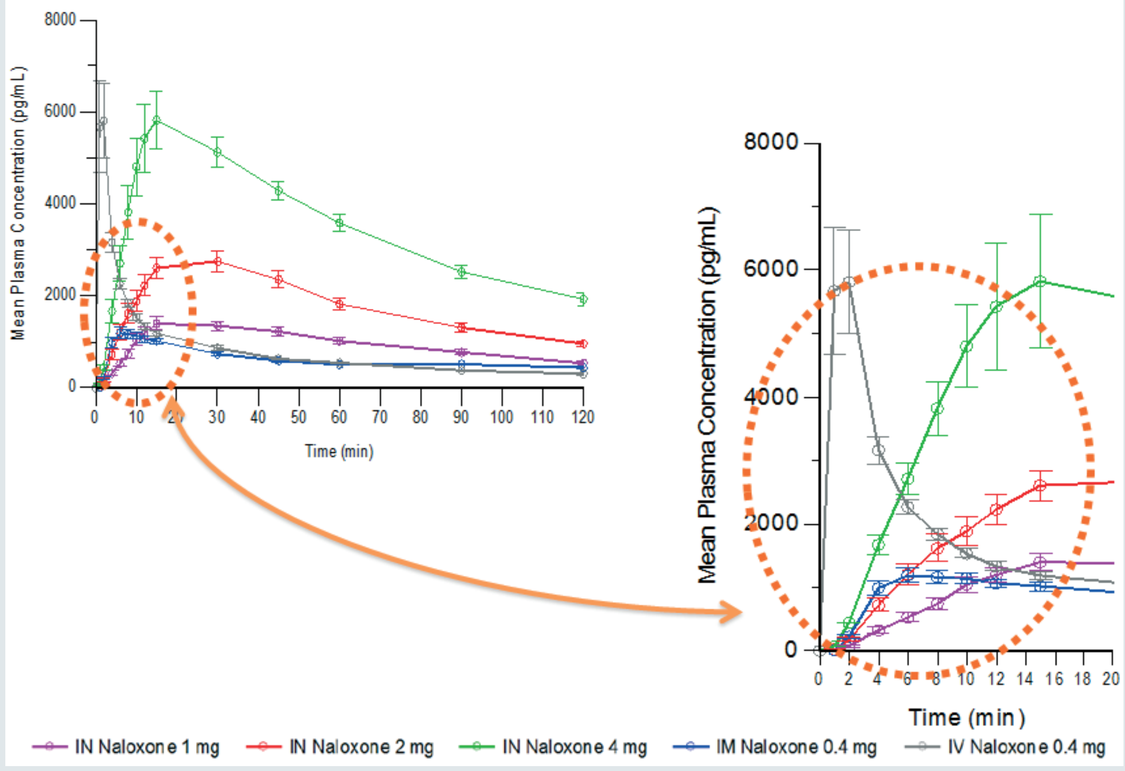
Table 1 | Pharmacokinetic Parameters of Intranasal and Injectable Naloxone (mean values)

PK Parameter	IN 1mg	IN 2mg	IN 4mg	IM 0.4mg	IV 0.4mg
AUCt (pg*h/ml)*	2561.10	4858.94	10006.97	2005.65	2006.34
AUCINF (pg*h/ml)*	2690.78	4965.00	10070.19	2118.03	2100.32
AUCp (pg*h/mL)*	51.78	109.82	265.94	114.00	440.24
Cmax (pg/ml)*	1512	2867	6019	1273	5943
LambdaZ (h^{-1})	0.55	0.53	0.44	0.53	0.57
t1/2Z (min)	80	85	101	81	75
HVD (min)	79	76	75	65	8
T50% (min)	10	10	9	4	1
Tmax (min)^	15	30	15	10	2
F_{IM}% (AUCINF)	50.44	45.46	46.20	N/A	N/A
F_{IM}% (AUCt)	50.81	47.08	48.34	N/A	N/A

Annotations: AUCt= area under the curve (AUC) up to last measurable time point; AUCINF= AUC up to infinity; AUCp= partial AUC with cut-off at Tmax of reference; Cmax= maximum observed plasma concentration; LambdaZ= terminal phase rate constant; t1/2Z= terminal phase half-life; HVD= half-value duration; T50%=time to 50% of Cmax; Tmax= time to Cmax; F_{IM}%= bioavailability relative to intramuscular reference; *geometric mean; ^median.

Figure 1 | Plasma Naloxone Levels: Dosing to 2 Hours (mean ± standard error)



Background

Take-home naloxone (THN) can prevent fatal outcome from heroin/opioid overdose (WHO, 2014) but pre-provision is difficult because naloxone is given by injection. Following years of off-label use of untested improvised nasal naloxone kits, the FDA approved a first nasal spray in the US in late 2015 (FDA, 2015). For nasal sprays, the dose must be adequate, rapid-acting, but not excessive to avoid 'over-antagonism' (Hertz, 2012; Neale & Strang, 2016; UKMi, 2016). We report on the pharmacokinetics (PK) of a concentrated nasal spray currently in development (see photo).

Aims

Primary objectives:

- To assess pharmacokinetics of intranasal (IN) naloxone
- To compare early partial systemic exposure with IN vs intramuscular (IM) and intravenous (IV) naloxone.

Secondary objective:

- To determine IN bioavailability relative to IM naloxone.

Method

Ethics approval was granted by the South Central – Berkshire B REC. A PK study (open-label, randomised 5-way crossover; EudraCT: 2015-004493-15) in healthy volunteers compared highly-concentrated IN naloxone (10mg/ml; 20mg/ml) at 3 doses (1mg; 2mg; 4mg (as 2x2mg)) with 0.4mg IM (primary reference) and also 0.4mg IV naloxone. Blood collection included intense sampling over the first 15 minutes. Special attention was paid to early uptake, including partial AUC from time of dosing to median Tmax of IM naloxone and the time taken to reach 50% of Cmax (T50%).

Results

(a) Subjects: 32 completing healthy volunteers (age 20-54; 10 female).
(b) PK profiles:

- IN naloxone was characterised by approximately 50% bioavailability relative to IM (means of 47-51% across three nasal doses; Table 1); thus 1mg IN dose had slightly higher AUC than 0.4mg IM or IV.
- Within 10 minutes post-dosing, the 2mg IN dose most closely followed the 0.4mg IM curve.
- IN reached maximum plasma levels at 15-30 minutes (Tmax) and rapidly achieved plasma levels >50% of peak concentrations (T50%) at 9-10 minutes (slightly slower than with IM and IV; see Table 1, Fig 1).
- IM was characterised by peak plasma levels at a median of 10 minutes (Tmax) and rapid achievement of plasma levels >50% of peak concentrations (T50%) by 4 minutes post-dose, with gradual decay thereafter.
- IM naloxone (primary reference) appeared to be almost completely absorbed (98% bioavailability relative to IV).
- IV was characterised by an extremely rapid spike of plasma concentration, reaching peak at 2 minutes (Tmax), followed by rapid decay over the next 10 minutes and gradual decay thereafter.

Discussion

Overall, concentrated nasal naloxone appears to be well-absorbed (approx. 50% bioavailability relative to IM) and, after dose-adjustment, displays similar early-onset time-course. The 2mg IN dose gives speed of onset comparable to 0.4mg IM through the first 10 minutes, and then ongoing plasma levels for the next couple of hours at twice the level maintained by the IM dose.

Conclusions

The 2mg IN dose appears to be a viable alternative to a 0.4mg IM injection. With circumnavigation of obstacles for injectable naloxone, clinicians and policymakers may see advantages with IN naloxone for THN programs.

References

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Declaration of sponsor and interests

This research was financially supported by Mundipharma Research Ltd, Cambridge, UK, by whom it was designed in consultation with JS, and conducted at Richmond Pharmacology Ltd, St. George's University of London, UK, under contract from Mundipharma Research Ltd. Data were evaluated jointly by the authors and the sponsor. JW, BB, HJ, GM and KS are employees of Mundipharma Research Ltd. UL is an employee of Richmond Pharmacology Ltd and was the Principal Investigator for this study.
JS and RM are employed by the university King's College London (KCL), UK. JS is a researcher and clinician who has worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products), and from whom he and his employer (KCL) have received research funding, honoraria, travel costs and/or consultancy payments, including from Mundipharma to KCL for JS' time and input to the study reported above. JS has also been named as an inventor in an earlier patent application filed by by Euro-Celtique S.A. (an Independent Associated Company of Mundipharma Research Limited) and entitled 'Intranasal Pharmaceutical Dosage Forms comprising Naloxone'. For fuller account for JS, see www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. KCL (employer for both JS and RM) has separately registered intellectual property on a novel buccal naloxone formulation with which JS and RM are involved. JS is supported by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and KCL.
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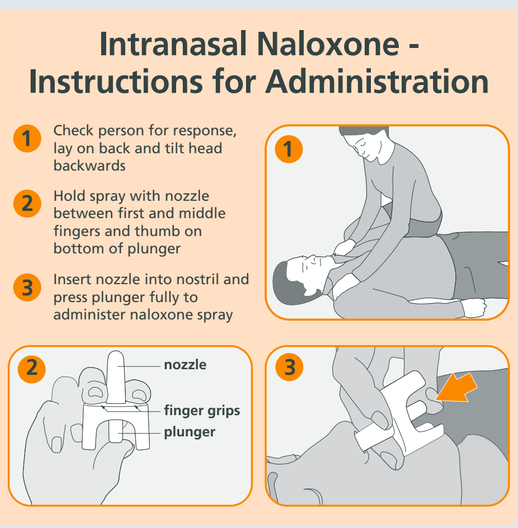

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