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The pharmacokinetics of intranasal droperidol in volunteers characterised via population modelling

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Abstract

Background: Droperidol is used parenterally to treat nausea and vomiting, migraine and acute behavioural disturbance. Intranasal use is not reported for droperidol. Intranasal drug administration reduces need for intravenous line placement and risk of needle-stick.

Objective: To model population pharmacokinetics of intranasal droperidol.

Method: Single doses of intranasal and intravenous droperidol (0.02 mg/kg) were studied in an open-label crossover-trial in seven volunteers with a 1-week washout period. Blood samples collected over 10-h were analysed by liquid chromatography tandem mass spectrometer. Droperidol plasma concentrations following intravenous and intranasal administration were subjected to non-compartmental analysis and population pharmacokinetic modelling using S-ADAPT. Monte Carlo simulations were conducted for various potential intranasal dosage regimens.

Results: The droperidol concentration-time profiles following intravenous and intranasal administration were best described by a model with two equilibrating disposition compartments and linear elimination. The apparent elimination clearance for intranasal dosing was 87.9 L/h and apparent central volume of distribution 18.2 L. Monte Carlo simulations of 5 mg droperidol (corresponding to the maximum volume that can be practically administered intranasal at a time) given intranasally at 0 and 5 min or 0 and 10 min indicated peak concentrations would reach those seen at 25 min after single intravenous administration of 1.5 mg. No adverse clinical effects or QT interval prolongation were observed.

Conclusion: Given the reduced bioavailability of intranasal droperidol, Monte Carlo simulations suggested that it could potentially be used at a higher dose (2.5–5 mg) than currently used intravenously in clinical trials assessing the effectiveness in treatment of nausea, vomiting and migraine.

Keywords

Population pharmacokinetics, droperidol, intranasal, antipsychotics, pharmacokinetics

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Introduction

Droperidol is a butyrophenone antipsychotic drug that is widely used for the management of nausea and vomiting, acute psychosis and acute behavioural disturbance (ABD). More recently, it has been shown to be effective in the management of migraine and vertigo.[1] Parenteral administration of droperidol is popular in the acute care setting due to a predictable and rapid onset of effect.[2,3] It is administered either intravenously (IV) or intramuscularly (IM) at recommended doses of 0.625–2.5 mg for anti-emesis and up to 10 mg for ABD.

The intranasal (IN) route of drug administration has many advantages. It has the potential to eliminate the pain, anxiety

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Table 1. Weight-based calculation for intranasal droperidol dosing.

Weight (kg)	Dose in mg and (diluted drug volume)	Volume administered to each nare
50–62.5	1 mg (0.4 mL)	One nare
62.6–75	1.5 mg (0.6 mL)	0.30 mL to each nare
75.1–87.5	1.7 mg (0.7 mL)	0.35 mL to each nare
87.6–100	2 mg (0.8 mL)	0.4 mL to each nare

and distress associated with needle insertion for IV or IM drug delivery. The risk of needle-stick injury and blood-borne infection is also minimised by the use of needleless systems. In addition, drug administration can occur more quickly than IV administration, as there is no need to spend time siting a cannula.[4] The nasal cavity has a rich vascular plexus with a large mucosal surface area, meaning drugs are rapidly absorbed into the bloodstream with a shorter time to peak concentration than seen with oral or intramuscular administration. Bioavailability may be higher with IN than oral dosing for some drugs, as there is no gastrointestinal tract degradation or hepatic first-pass metabolism.[5] IN drug delivery is utilised for a number of drugs in the clinical, acute care setting. In particular, fentanyl, ketamine, and midazolam are all used intranasally in emergency medicine practice.

The IN route of administration has not been previously investigated for droperidol. In a pharmacokinetic (PK) study investigating the bioavailability of IN haloperidol, therapeutic concentrations were attained.[6] Droperidol and haloperidol are structurally similar butyrophenones. We hypothesise that IN droperidol will display similar PK characteristics to those of haloperidol. As a result, if the PK profile is favourable, droperidol may be a useful drug to consider for clinical trials of IN treatment of ABD and anti-emesis.

We undertook a study to assess the PK of low-dose IN droperidol and subsequently performed population PK modelling and Monte Carlo simulations to predict serum concentrations at higher doses that might also be used in the clinical setting for treatment of nausea, vomiting and ABD.

Method

Study design

The study was an open-label crossover volunteer study comparing the PK of a single dose of IV droperidol to a single dose of IN droperidol in healthy male volunteers. The study was conducted between November 2014 and April 2015. The Monash Health Human Research Ethics Committee granted ethics approval (approval no: 14127A). The trial was registered with the ANZCTR Clinical Trials Registry (ACTRN12614000514606).

Seven healthy male volunteers were recruited. Inclusion criteria were as follows: age between 18 and 55 years and body weight >50 kg and <100 kg with body mass index (BMI) <28. Exclusion criteria were as follows: allergy to droperidol, previous history of any dystonic reaction to medications, abnormal nasal anatomy, previous nasal surgery, or nasal trauma that may interfere with administration or absorption of IN medication, current or recent upper respiratory tract infection, use of any prescription or non-prescription drugs that may affect droperidol metabolism or nasal physiology (vasoconstrictors, e.g. phenylephrine) within the past 7 days, treatment with medication known to prolong the QT interval, absolute QT calculated as the average of three limb leads and three chest leads (V2–V4) QT interval duration, abnormal 12-lead electrocardiography (ECG) on screening with the corrected QT interval (QTc) greater than 480 ms using Sagie regression QTc calculation formula and correlated with Isbister QT-heart rate pair nomogram,[7] any medical or mental health disorder or previous history of antipsychotic medication use. Subjects abstained from alcohol and caffeine for 24 h prior to and during the study period. The study was performed in a non-clinical area of the Emergency Department of Dandenong Hospital with haemodynamic monitoring and critical care facilities available in the unlikely event of an adverse drug reaction or adverse event in relation to droperidol administration. Each subject had an 18G IV cannula inserted in order to administer IV droperidol and for blood sampling.

Study treatment

Subjects all initially received IN droperidol followed by a 1-week wash-out period and subsequently administration of IV droperidol. The droperidol formulation used was as a 10 mg/2 mL solution (DORM®, Phebra, Australia).

IN droperidol was administered using an LMA Mucosal Atomiser Device (MAD, Teleflex Medical, Burnley, Victoria, Australia). Droperidol was diluted to a concentration of 0.25 mg per 0.1 mL. The dose was calculated in 12.5 kg weight bands as close to 0.02 mg/kg as possible from 50 to 100 kg as shown in Table 1.

The drug was drawn up into separate 1 mL syringes for each nare. The volume drawn up in each syringe was slightly greater (0.2 mL) than that to be injected to allow for priming of the MAD device to remove dead space from this and prevent drug loss in the dead space of this device. Prior to drug administration, subjects were asked to blow their nose. The drug was administered with the subjects in a semi-recumbent, 45°head-up position. After the droperidol was administered, the subjects remained in this position for 10 min.

IV droperidol was administered at a dose of 0.02 mg/kg via the IV cannula diluted to a volume of 10 mL with 0.9% saline solution as a slow IV injection over 10 min. The cannula was flushed with another 20 mL of 0.9% saline. The cannula was then used for blood sampling.

Subjects remained supine for 2 h following droperidol administration and were observed within the study area

throughout the duration of the protocol. After the last blood sample the cannula was removed, and the subjects were monitored for a further 15 minutes.

Drug administration occurred in the morning following an overnight fast of a minimum of 6 h, and the subjects continued to fast until 2 h post-droperidol dose. Water and non-caffeinated beverages were permitted throughout.

Subject's vital signs (pulse and blood pressure) and sedation score (Richmond Agitation Sedation Scale) were recorded immediately prior to droperidol administration and following droperidol administration at 15, 30, 60 min, and hourly to 4 h, and then two hourly to 10 h after administration. Continuous ECG monitoring was performed for the first 4 h post-drug administration. A 12-lead ECG was performed prior to drug administration, 2 h after drug administration and at the completion of each study arm for QT interval comparison. Subjects were questioned about any adverse events experienced during the study. In addition, they were provided with an information sheet describing any delayed adverse events and a contact number for the study doctor.

Sample size calculation for initial PK study

Sample size calculation for the volunteer cohort was based on the only comparable data available from the haloperidol study by Miller et al, (2008). In this study, mean peak haloperidol concentration in four subjects post-IN administration was one-third of that after intravenous administration with a standard deviation of ±20 ng/mL. For this study, using an expected peak droperidol concentration assumption as above for the IV group, a calculated sample size of n = 7 subjects in the IN and IV arms would result in an expected mean peak serum concentration of droperidol in the IN group of around 60 ng/mL with a 95% confidence interval (CI) of ±15 ng/mL. ((CIs and sample size were calculated using STATA statistical software using binomial CIs).

Blood collection and droperidol assay

Serial blood samples were collected for droperidol assays through the IV cannula. One blood sample was collected prior to droperidol administration, then samples were collected at 15, 30, 45, 60, 120 min and then at 4, 6, 8 and 10 h post-administration (i.e. post-end of the 10 min injection for IV dosing). For each sample, 4 mL of blood/fluid was removed from the cannula using a 5 mL syringe and discarded. Then a 5 mL sample of blood was collected in an ethylenediaminetetraacetic acid (EDTA) blood sample tube. Once the sample was collected, a 5 mL 0.9% saline flush was used to purge the cannula. The blood samples were labelled and stored at −20°C for subsequent batch analysis.

Droperidol blood concentrations were assayed at the Victorian Institute for Forensic Medicine (VIFM, Southbank, Victoria, Australia). Extracts of the EDTA blood specimens were analysed by an ultra high-pressure liquid chromatography tandem mass spectrometric (UHPLC-MS/MS) method in positive electrospray ionisation (ESI) mode. Drug detection was confirmed by the presence of three transitions of a precursor ion for droperidol (retention time 2.04 min, transitions monitored (amu): 380.0→122.9 (quantifier) 380.0→165.0 (qualifier 1), 380.0→194.0 (qualifier 2)). A deuterated internal standard, haloperidol-d4, was acquired using two transitions of the precursor ion. This was used to calculate droperidol concentrations in each sample using a six point curve ranging from 0.1, 1, 5, 10, 50, 100 ng/mL. The lower limit of quantification was 0.1 ng/mL and was demonstrated to show a signal to noise ratio greater than 10:1. Internally prepared quality controls (droperidol spiked in blood) were analysed after the calibration curve and every five samples. Quality control calculated concentrations were spiked at 25 ng/L and deemed acceptable if within ± 30% of the target concentration.

PK analysis

Non-compartmental analysis (NCA) was performed utilising EquivTest PK (Statistical Solutions Ltd, Saugus, MA, USA). The plasma concentrations of droperidol following IV and IN administration were co-modelled by population PK analysis. For comparison, the concentrations following each administration route were also modelled separately. Modelling was performed using S-ADAPT (version 1.57) with an importance sampling Monte Carlo Parametric Expectation Maximisation algorithm (p method = 4).[8] S-ADAPT-TRAN was utilised for pre- and post-processing.[8,9] Models with one, two and three disposition compartments and with and without a lag-compartment for absorption of droperidol following IN administration, were evaluated. The inter-individual variability (IIV) between study subjects was described by a log-normal distribution, except for bioavailability (F), for which it was described by a logistic transformation.

Models with full, partial and diagonal variance–covariance matrices were evaluated. The residual unexplained variability was described by a combined proportional plus additive error model. Candidate models were compared based on individual fittings to the concentration-time profiles, observed versus individual-fitted and observed versus population-fitted plots, visual predictive checks, the normalised prediction distribution error and the S-ADAPT objective function (equivalent to −1 log-likelihood).

Monte Carlo simulations, including IIV, were conducted based on the final population PK model for various dosing regimens for IN administration assuming dose proportionality.[9] The simulated regimens were as follows: single doses of 1.5, 2.5 or 5 mg droperidol, 5 mg droperidol given at 0 min followed by a second dose of 5 mg given at 5 or 10 min, and 5 mg droperidol given at 0 min followed by a second dose of

Table 2. Droperidol non-compartmental PK parameters.

Parameter	Units	Median (range)	
		IV	IN
Maximum concentration (C_{max})	μg/L	26.6[a] (14.5–85.9)	6.5 (2.6–8.0)
Time of C_{max} (T_{max})	H	0.25 (0.25–0.25)[b]	0.50 (0.50–1.0)
Area under the curve from 0 to 10 h (AUC_{0-10h})	μg h/L	40.0 (36.0–79.6)	18.7 (8.79–33.4)
Area under the curve from 0 h to infinity (AUC_{0-inf})	μg h/L	41.4 (37.3–81.1)	19.2 (9.4–35.6)
Bioavailability (F)	%		41.4 (15.0–58.6)
Clearance (CL)	L/h	33.8 (17.3–48.5)	
Apparent clearance (CL/F)	L/h		82.7 (47.8–160)
Elimination half-life ($T_{1/2}$)	H	2.06 (1.87–2.15)	2.38 (1.80–2.75)

IN: intranasal; IV: intravenous.
[a]Concentration at first sampling time point, actual C_{max} at the end of administration would have been higher.
[b]First sampling time point, actual C_{max} would have occurred at the end of administration.

5 mg given at 0.5 or 1 h. The largest dose simulated for IN administration was 5 mg, as 0.5 mL (which corresponds to 2.5 mg droperidol) is the maximum volume of droperidol formulation that can practically be given IN per nare. Larger volumes have a high risk of partial mucosal absorption and a significant proportion of the administered dose may be swallowed. For each dosage regimen, 7000 virtual subjects were simulated using NONMEM (version 7).

Results

All of the recruited seven healthy male volunteers completed both arms of the study. Median age was 23 (range: 20–43) years, median weight 73 (range: 65–98) kg and median height 180 (range: 170–195) cm. There were no adverse clinical events in any subject. All subjects reported mild degrees of sedation and sleepiness in the initial 1–2 h post-dosing with both routes of administration. However, median Richmond Agitation Sedation Score (RASS) was only recorded as −1 at 30, 45 and 60 min post-IV administration and 0 at every other time point. Median RASS was 0 at every time point for post-IN administration. All volunteers had 12-lead ECGs recorded at 0, 2 and 10 h. There was no QT prolongation at any time point. The average droperidol dose was 1.53 mg (95% CI: 1.3–1.7) for the IV and 1.63 mg (95% CI: 1.4–1.8) for the IN arms of the study.

NCA results following IV dosing showed a median total body clearance (CL) of 33.8 L/h and an elimination half-life of 2.1 h (Table 2). The apparent median clearance following IN dosing was 82.7 L/h with a median elimination half-life of 2.4 h. The median IN bioavailability, based on NCA, was 40%.

The droperidol concentration-time profiles following IV and IN administration were best described by a model with two equilibrating disposition compartments and linear elimination. Absorption of droperidol following IN dosing was linear and was best described by inclusion of an additional lag-compartment. Inclusion of this lag-compartment significantly improved the S-ADAPT objective function (by 12.9 points). Further complexities did not improve the model fit. A partial variance–covariance matrix for clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2) and distribution clearance (CLd) was incorporated. Plots of the individual and population predicted versus observed droperidol concentrations demonstrated that the fits were unbiased for both routes of administration. The visual predictive checks (Figure 1) showed very good predictive performance of the model for both IV and IN dosing and goodness-of-fit plots were unbiased (Figure 2). The population PK parameter estimates are reported in Table 3. All apparent CL and volume parameter estimates for IN dosing were similar between the model that included both IV and IN data and the model based on IN data only (Table 3 including footnotes).

The Monte Carlo simulation results are presented in Figures 3–5. In the single dose simulations at 1.5, 2.5 and 5 mg (Figure 3), even the 90th percentile of the predicted peak droperidol concentrations did not reach the average concentration seen at 25 min following the start of an IV infusion at 1.5 mg (Figure 1). However, the repeat dose simulations at 5 mg indicated peak droperidol concentrations reaching those seen at 25 min after the IV administration in the volunteers and in the visual predictive checks. In particular, the addition of a second dose of IN droperidol 5 or 10 min after the first dose resulted in relatively high peak concentrations for the 90th percentile of the simulated subjects (Figure 4). In addition, simulation of a delayed repeat dose regimen, where the second dose of droperidol was given with a lag of 1 h, resulted in biphasic peaking of droperidol concentration (Figure 5). A consort diagram for the INKDROP cross-over volunteer study determining the pharmacokinetics of intranasal and intravenous droperidol is shown in Figure 6.

Discussion

The utility of the IN route for drug administration is well described in the emergency department and pre-hospital settings, particularly in the paediatric population. It provides an

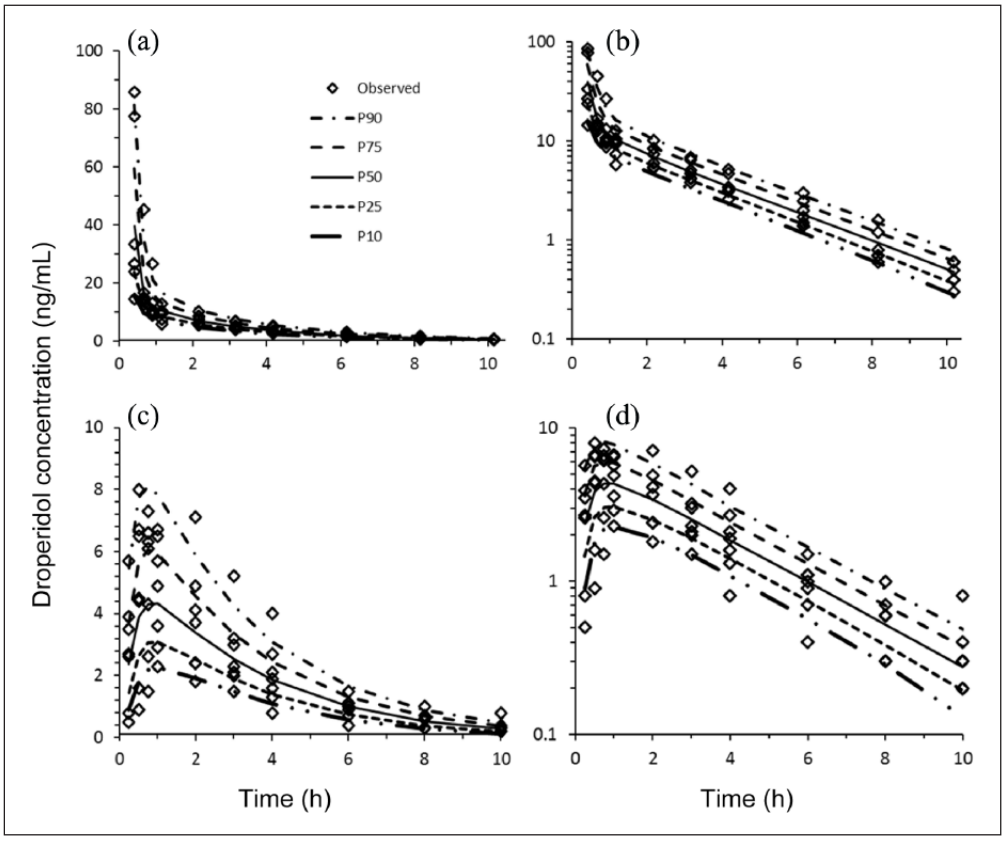

Figure 1. Visual predictive checks of IV ((a) and (b), on linear and log-scale, respectively) and IN ((c) and (d)) droperidol concentration versus time showing observed data and the 10th, 25th, 50th, 75th and 90th percentiles of the predicted concentrations following an average per subject droperidol dose of 1.53 mg IV and 1.63 mg IN.

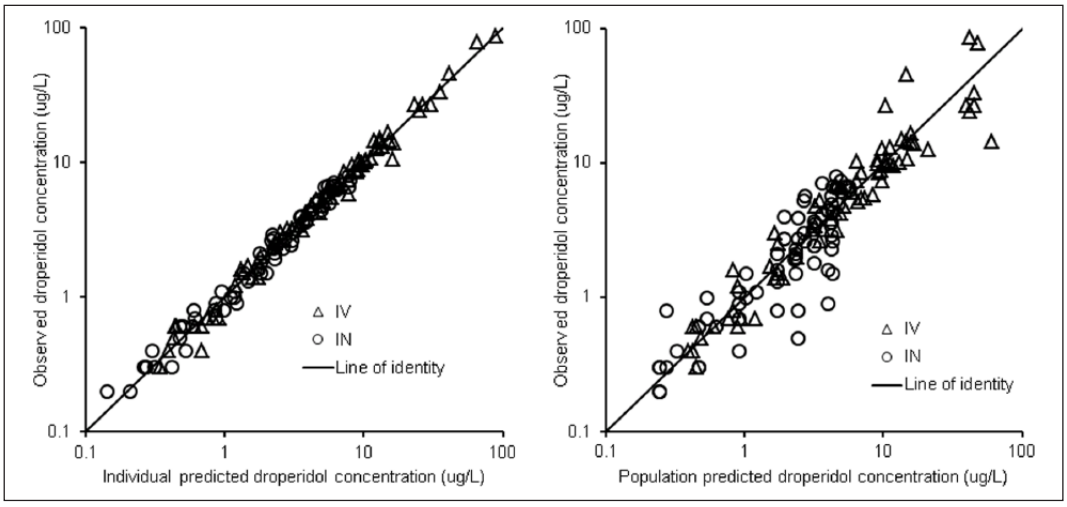

Figure 2. Individual (left) and population (right) predicted droperidol concentrations versus observed droperidol concentrations.

easy and rapid route of administration that does not need prior IV cannula insertion. Analgesic agents, such as fentanyl and ketamine can be rapidly delivered by this route.[10,11] Similarly, naloxone can be given IN to reverse opioid toxicity.[12,13] Midazolam, a short acting benzodiazepine, can also be given IN for sedation and the acute management of seizures. Parenteral droperidol, in low doses, has been extensively described in the treatment of post-operative and

Table 3. Droperidol population PK parameter estimates for the final model incorporating both IN and IV data.

Parameter	Units	Estimate (SE%)	IIV (%CV) or 5th to 95th percentile (P5–P95)
Total body clearance (CL)	L/h	15.3[a](13.9)	29.6%
Central volume of distribution (V1)	L	3.16 (34.3)	85.5%
Peripheral volume of distribution (V2)	L	16.9 (23.1)	43.6%
Distribution clearance (CLd)	L/h	9.66 (30.0)	57%
Absorption rate constant (ka)	h^{-1}	0.517 (11.5)	13.1%
Rate constant for lag time (klag)	h^{-1}	5.18 (27.6)	47.7%
Bioavailability (F)	%	17.4[a](15.0)	11.6–25.3
Terminal half-life ($T_{1/2,}\beta$)	h	2.0	
CL/F for IN dosing	L/h	87.9[b]	
V1/F for IN dosing	L	18.2[c]	
V2/F for IN dosing	L	97.1[d]	
CLd/F for IN dosing	L/h	55.5[e]	
CVcp	%	13.2	
SDcp	μg/L	0.040	

IIV: inter-individual variability; CV: coefficient of variation; CVcp: proportional residual error; SDcp: additive residual error; SE%: standard error of the population estimate.
[a]Most likely the CL following IV dosing was underestimated by the population PK analysis due to the relatively late timing of the first sample in the IV arm and therefore F is also likely underestimated.
[b]Calculated as the ratio of the population estimates for CL and F; the CL/F when modelling only the IN data was 84.6 L/h.
[c]Calculated as the ratio of the population estimates for V1 and F; the V1/F when modelling only the IN data was 11.3 L.
[d]Calculated as the ratio of the population estimates for V2 and F; the V2/F when modelling only the IN data was 119 L.
[e]Calculated as the ratio of the population estimates for CLd and F; the CLd/F when modelling only the IN data was 40.8 L/h.

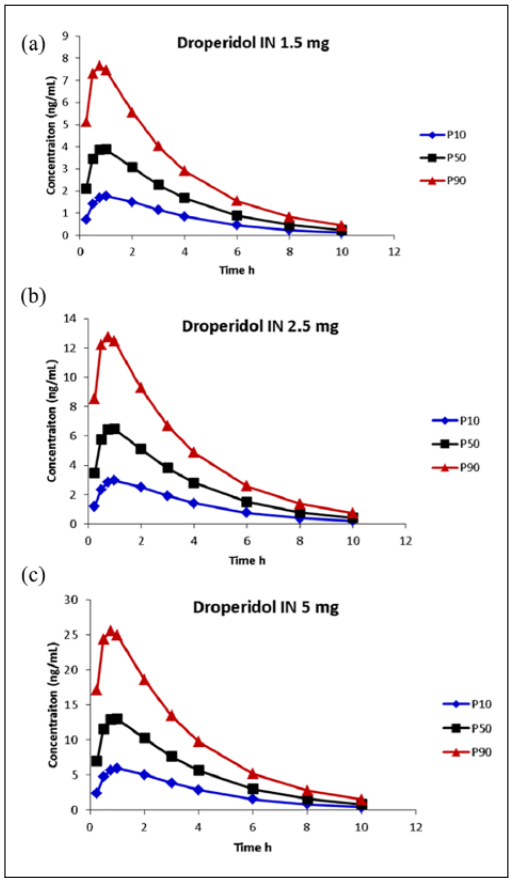

Figure 3. Single dose simulations of IN droperidol administration at 1.5 mg (a), 2.5 mg (b) and 5 mg (c) presenting the median (P50) and the 10th (P10) and 90th (P90) percentiles of the predicted concentrations.

chemotherapy-induced nausea and vomiting, as well as in the treatment of migraine. While other oral, sub-lingual and parenteral medications can be used to treat nausea and vomiting, the IN route of delivery for droperidol may be an alternative to consider for symptom control in these patient groups.

This is the first study to characterise the PK of droperidol after IN administration. We found that droperidol serum concentrations following a relatively low dose given IN peaked within an hour of administration and were within the range observed during and after low-dose IV infusion reported previously.[14] The terminal elimination half-life of around 2 h that we observed, for both IN and IV dosing, matches well with previously published results.[15] In addition, droperidol was detectable for the whole 10 h observation period of the study following IN administration. The full time-course following IN administration, which was the main focus of the study, was well characterised by the sampling schedule.

The median bioavailability of IN compared to IV dosing was calculated at 40% via NCA. This bioavailability is similar to that seen in a comparable study, where 2.5 mg of haloperidol was administered IN to volunteers (bioavailability 48%).[6] However, the value IN bioavailability of 40%, calculated from NCA, in this study was likely overestimated. This is due to a lack of droperidol sampling data during the first 15 min after the end of the 10-min IV injection, a period where droperidol concentrations are likely to have declined rapidly. As a result, the CL in the IV arm of the study was likely overestimated by NCA, while the CL following IN administration was well characterised. Despite this, the median total body CL following IV dosing calculated via NCA at 33.8 L/h was comparable to the CL of 39.4 L/h reported by Gupta et al.[14] in healthy volunteers during a

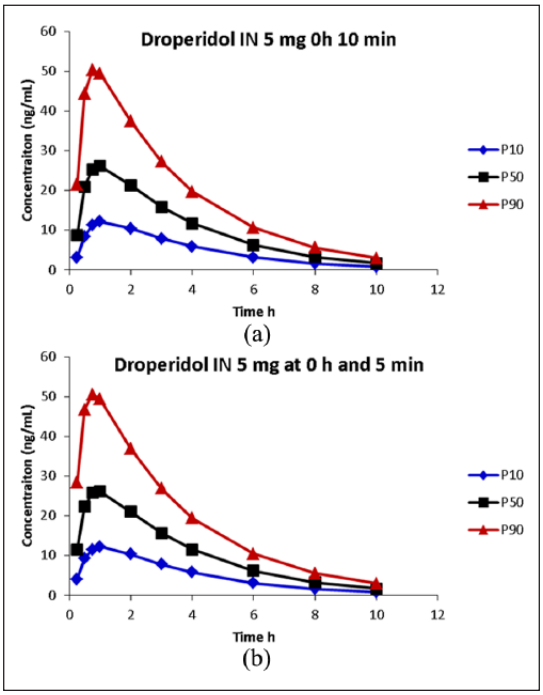

Figure 4. Repeat dose droperidol simulations where 5 mg is administered at time-0 and then a further dose of 5 mg given 5 min (a) and 10 min (b) later. The median (P50) and the 10th (P10) and 90th (P90) percentiles of the predicted concentrations are represented on the figures. Note that the P90 concentration peak in both cases approaches the range seen with IV dosing in this study.

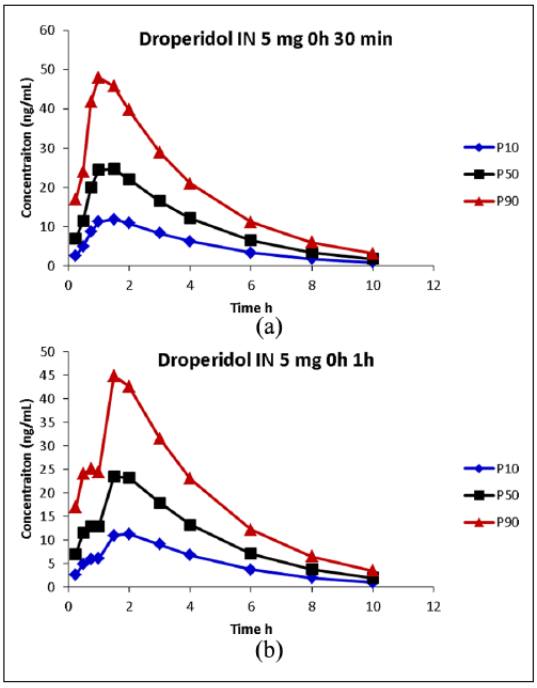

Figure 5. Repeat dose droperidol simulations where 5 mg is administered at time-0 and then a further dose of 5 mg given 30 min (a) and 1 h later (b). The median (P50) and the 10th (P10) and 90th (P90) percentiles of the predicted concentrations are represented on the figures. Note that the P90 concentration peak after the second dose of droperidol, in both cases, approaches the range seen with IV dosing in this study.

3 mg droperidol dose given as a 24 h IV infusion. Two other clinical studies reported slightly higher average CLs following IV doses of 5–15 mg droperidol in anaesthetised patients.[16,17]

Population modelling achieved a very good predictive performance for both the IV and IN data. In contrast to NCA, it predicted and took into account likely plasma concentrations during the first 25 min after the start of the IV infusion. However, it may have over-predicted the true droperidol concentrations during that time. If this was the case, the IN bioavailability may in reality lie in between the model estimated 17% (Table 3) and the 40% from NCA. However, this potential limitation does not impact on the model predictions for the IN administration, that is, the main aim of the analysis.

Observed droperidol concentrations were available to characterise the full concentration-time profile following IN dosing (Figure 1), and these are the driver for the pharmacological effect. Also, the apparent CLs following IN dosing were 87.9 L/h when co-modelling IV and IN data, 84.6 L/h when modelling only IN data and 82.7 L/h based on NCA, thus were very similar between all of the different approaches.

Notably, we chose an IV dose in the range that is commonly recommended for the treatment of nausea and vomiting (0.5–2 mg), in the clinical setting. This equates to around 1.5 mg (0.02 mg/kg) for a 75-kg adult. We aimed to see whether similar serum concentrations would be achieved after IN administration. While serum droperidol concentrations were significantly lower with IN delivery, the study was not designed to correlate this with any clinical outcome in the treatment of nausea or vomiting. It is also unknown at what threshold concentration droperidol may exert inhibitory effects on nausea and vomiting. Importantly, all our volunteers exhibited some degree of subjective drowsiness within the hour following IN administration, correlating with the time of peak concentration and suggesting a mild sedative effect at this low dose. It is unknown whether there is a correlation between the development of drowsiness and antiemetic effect and there are no data correlating antiemetic effect with serum concentration of droperidol.

Further dose-finding clinical studies of IN droperidol are required in the setting of nausea and vomiting to assess the correlation between PK and pharmacodynamic effect for this indication. Given the relatively low concentrations observed following IN dosing compared to IV administration, it is possible that a larger dose may be required by the IN route for treatment of nausea and vomiting than the one we used in the volunteers. As a result, either 2.5 or 5 mg are likely to be appropriate starting doses for clinical trials.

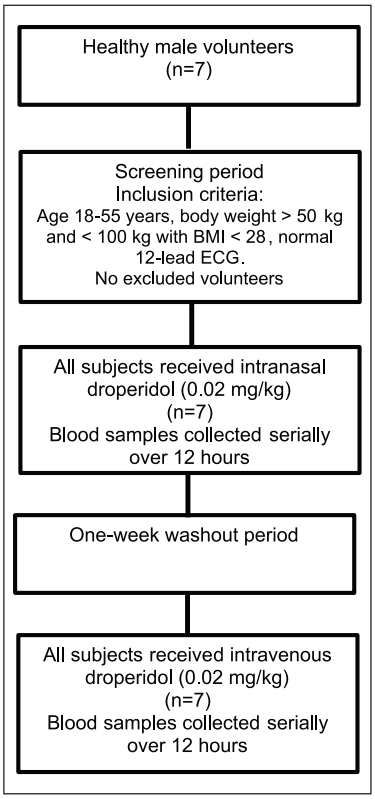

Figure 6. Consort diagram for INKDROP cross-over volunteer study determining the pharmacokinetics of intranasal and intravenous droperidol.

The population analysis indicated linear PK within the concentration range observed following IV and IN administration in this study. The serum concentrations predicted from the IN population PK model after administration of a second dose at 5 and 10 min after the first dose, suggest this dosing strategy may be a useful way to titrate to a desired clinical effect. Furthermore, we used a relatively small dose of droperidol and diluted this to standardise IN administration volume. It is possible that administration of undiluted drug could result in a greater concentration gradient across the mucosal barrier and thus increased systemic absorption. As a result, administration of a larger dose of undiluted drug may exert more of a clinical effect. A clinical trial at varying doses could clarify this issue.

Other than expected mild sedation, we did not observe any adverse effects with our droperidol dosing. There were no extrapyramidal side effects in the volunteers and no effect on the QT interval after IV or IN dosing. In larger studies reporting IV droperidol use, common side effects included unwanted deeper levels of sedation and occasional episodes of extrapyramidal dystonic reactions.

Currently, there are no data available that quantitatively correlate droperidol serum concentrations following any route of administration with clinical effect. Consequently, the only way to know whether IN droperidol is effective for the treatment of nausea and vomiting or migraine is to undertake a placebo-controlled dose escalation clinical trial. Our developed population PK model supports the design of such a clinical trial. Because of the limitations on IN volume, it is likely that droperidol cannot be administered in a high enough dose intranasally to be used for sedation purposes. Also, attempting to administer a drug intranasally to an agitated patient has significant practical challenges. The preparation of droperidol used, DORM, comes in a concentration of 5 mg/mL. The largest volume that can be given intranasally without significant risk of swallowing some of the dose is 0.5 mL. While it is possible to repeat the dose within a few minutes, from the population modelling study, it is unlikely that serum concentration will reach a high enough peak to sedate the agitated patient, even after repeated 5-mg doses.

Conclusion

Droperidol dosing, intranasally, resulted in comparatively low but persistently detectable serum concentrations after administration of a small dose to healthy volunteers. Subsequent population PK modelling suggested that administration of a larger dose would result in serum concentrations comparable to those seen with IV doses commonly used for the treatment of nausea, vomiting and migraine. IN drug administration provides a practical, non-invasive way of administering various medications. Further clinical study of droperidol by this route may be useful to determine its clinical effectiveness in the emergency setting.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

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Informed consent

Written informed consent was obtained from all subjects before the study.

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Trial registration

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