Comparison of the lung delivery of a cisplatin dry powder using endotracheal administration and nose-only inhalation in rats

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Introduction

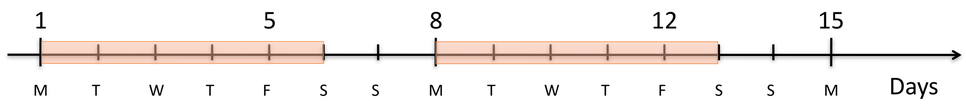
Preclinical studies remain necessary for the development of inhaled therapies.
The devices used for lung delivery of inhaled formulations to rodents can be classified as passive exposure devices (e.g., nose-only exposure) or endotracheal devices.

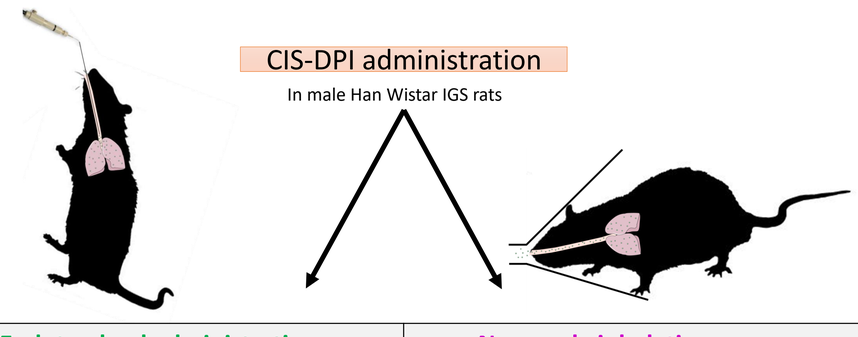
	Endotracheal administration	Nose-only inhalation exposure
Stage of the drug development	Early-stage	Advanced non-clinical stages (e;g., pivotal GLP studies)
Amount of drug formulation needed	Low (few milligrams)	High (hundreds of milligrams)
Specialised aerosol-generating equipment	Not required	Required
Sedation	Required	Not required
Generated aerosol	Forced and less physiological aerosol	Mimicking human physiological conditions with uniform deposition into the lungs
Drug delivery to the lungs	Precise dosing	Estimated dosing
Exposure of other routes	Avoid	Possible (nasopharynx and gastrointestinal tract)

Objectives

Compare the administration of a cisplatin dry powder for inhalation (CIS-DPI) developed previously [1] to healthy rats using endotracheal administration and nose-only inhalation exposure in terms of pharmacokinetics (PK) profiles and overall tolerance.

Material & methods





	Endotracheal administration	Nose-only inhalation exposure
Location	InhaTarget Therapeutics (Gosselies, Belgium)	Charles River (Edinburgh, UK)
Device	DP-3 insufflator device	Wright Dust Feed mechanism (aerosols for 30 min)
CIS-DPI dose levels	➔**0.2 mg/kg/day** cisplatin ➔**0.4 mg/kg/day** cisplatin ➔**0.8 mg/kg/day** cisplatin	➔**0.1 mg/kg/day** cisplatin ➔**0.2 mg/kg/day** cisplatin ➔**0.4 mg/kg/day** cisplatin (MTD = 0.46 mg/kg/day)
Blood on days 1, 5 and 12	For 0.4 mg/kg/day: ➔0 min, 10 min, 30 min, 60 min, 4h and 24h For 0.2 and 0.8 mg/kg/day: ➔0 min, 30 min and 60 min	-
Plasma	On days 1 and 12: ➔Terminal sampling for the 0.2 mg/kg/day group	On days 1, 5 and 12 for all groups: ➔0 min, 10 min, 30 min, 60 min, 4h and 24h
Lungs on days 1 and 12	For the 0.2 mg/kg/day group	All timepoints for the 0.2 mg/kg/day group
Platinum quantification method	Atomic absorption spectrometry (AAS) method	Inductively coupled plasma mass spectrometry (ICP-MS) method
LOD/LOQ of quantification	30/100 ng/mL in blood, 12/40 ng/mL in plasma, and 72/238 ng/g in lungs	0.83/2.5 ng/mL in plasma and 16.7/50 ng/g in lungs

Results & discussion

Overall tolerance

- For **nose-only administration:** A preliminary unpublished study of CIS-DPI at Charles River showed that dose escalation in rats using nose-only inhalation was limited to 0.46 mg/kg/day (identified as the MTD) by adverse reactions in the upper airways in the nasal cavity, although other non-adverse findings in the lungs (increased lung alveolar macrophages, alveolar mononuclear cell inflammation and increased lung weights) were observed ≥ 0.12 mg/kg/day.
- For **endotracheal administration:** Dose levels up to 0.98 mg/kg/day were well tolerated (no higher dose levels were studied) with only mild to moderate dose-dependent perivascular inflammation in the lungs.

Systemic exposure

Effect of increasing dose on platinum concentrations:

- For **nose-only inhalation**, in plasma: increased with the dose on days 1, 5, and 12, except on day 1 between the target doses of 0.1 and 0.2 mg/kg/day, where no increase was noted.
- For **endotracheal administration**, in blood: a consistent dose-dependent from day 1, day 5, and day 12

Effect of repeated dose on platinum concentrations:

- For **nose-only inhalation**, in plasma: At the same cisplatin dose level (0.4 mg/kg/day), the $AUC_{0\text{-}24h}$ increased between days 1 and 5 and was comparable between days 5 and 12.
- For **endotracheal administration**, in blood: the $AUC_{0\text{-}24h}$ (but also the C_{max}) increased with the number of administrations following endotracheal administration.

Table 1: Toxicokinetic parameters of platinum in plasma and blood following nose-only inhalation and endotracheal administration at 0.4 mg/kg/day cisplatin.

	Nose-only exposure – in plasma			Endotracheal administration – in blood		
	Day 1	Day 5	Day 12	Day 1	Day 5	Day 12
T_{max} (h)	0.67	1	0.7	0.5	4	4
C_{max} (ng/mL)	82.3	83.8	99.5	182.9	398.4	915.4
$AUC_{0min\text{-}24h}$ (ng.h/mL)	579	1,000	1,100	3,059	9,665	18,786

Platinum concentrations in blood versus plasma :

In the endotracheal study, from the same animals administered with 0.2 mg/kg/day cisplatin:

- On day 1, all concentrations in plasma were below the LOQ whereas C_{max} in blood was 89 ng/mL.
- On day 12, platinum concentrations in blood were higher than in plasma (C_{max} of 446 vs 106 ng/mL).

Platinum concentrations in plasma :

The platinum concentrations in plasma were overall higher following **endotracheal administration** at the different timepoints than **nose-only inhalation** at the same cisplatin dose (0.2 mg/kg/day) on day 12.

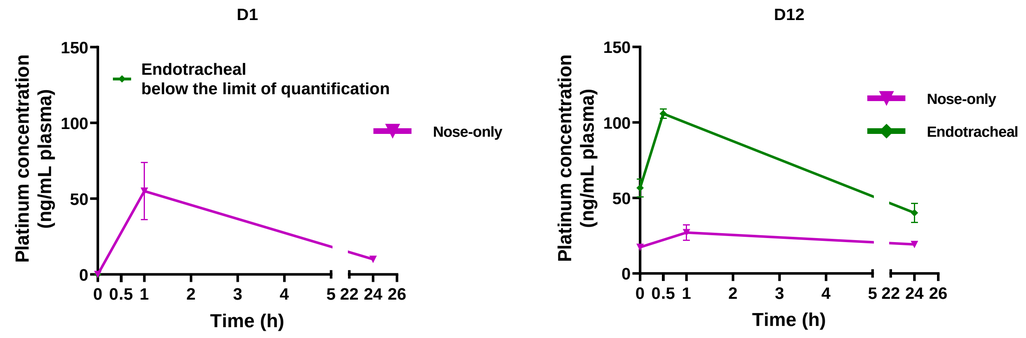


Figure 1: Platinum concentrations in plasma on days 1 and 12 at 0 min, 30 min (endotracheal route) and 60 min (nose-only inhalation, which includes the 30 minutes of exposure) and 24h following the last CIS-DPI administration (0.2 mg/kg/day). On day 1, platinum concentrations in plasma in the endotracheal study were below the LOQ (< 40 ng/mL). Mean ± SEM (n=2-4 per time point)

Lung exposure

Effect of repeated dose

The lung exposure to CIS-DPI increased from day 1 to day 12 following **both administration methods**, with C_{max} increased from 323 ng/g on day 1 to 1,265 ng/g on day 12 following **nose-only inhalation** and from 523.7 ng/g on day 1 to 1,687.4 ng/g on day 12 following **endotracheal administration**.

Platinum concentrations in the lungs

On day 1 and day 12, platinum concentrations in the lungs were from 1 to 1.6-fold higher following endotracheal administration than the nose-only inhalation at the same dose level at all timepoints except for the last measurement (i.e., 24 hours after the last administration of CIS-DPI on day 12) which were similar following both administration methods.

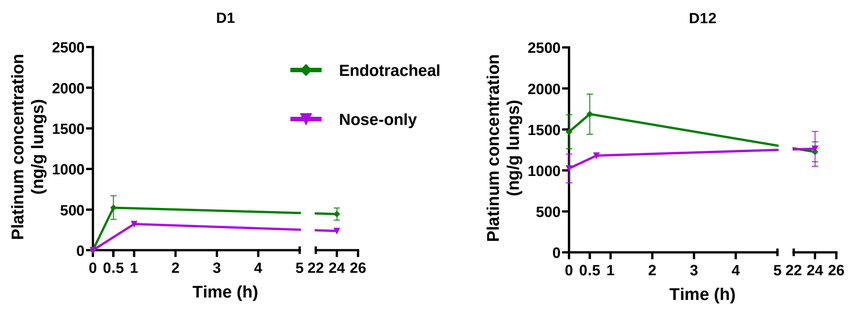


Figure 2: Pulmonary platinum concentrations (ng/g) on days 1 and 12 at 0 min, 30 min (endotracheal route) or 60 min (nose-only inhalation route post-start of the inhalation procedure) and 24h post-CIS-DPI administration (at 0.2 mg/kg/day). Mean ± SEM (n=2-4 per time point)

Conclusion

Endotracheal administration of CIS-DPI, by bypassing the upper airways, induced a higher deposition in the lungs and better tolerance in the respiratory tract at the same delivered dose level of cisplatin than the nose-only inhalation device.

Attention should be paid to the choice of device in preclinical studies of inhaled therapies as the administration route influences local and systemic exposure to the drug and, therefore, its efficacy and safety profile.

Reference

[1] S. Chraibi, R. Rosière, L. Larbanoix, P. Gérard, I. Hennia, S. Laurent, M. Vermeersch, K. Amighi and N. Wauthoz, "The combination of an innovative dry powder for inhalation and a standard cisplatin-based chemotherapy in view of therapeutic intensification against lung tumours," European Journal of Pharmaceutics and Biopharmaceutics, vol. 164, pp. 93–104, Jul. 2021, doi: 10.1016/j.ejpb.2021.04.018.

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