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SHORT REPORT

Pharmacokinetics of intravenous and inhaled salbutamol and tobramycin: An exploratory study to investigate the potential of exhaled breath condensate as a matrix for pharmacokinetic analysis

Matthijs D. Kruizinga[1] | Willem A.J. Birkhoff[1] | Michiel J. van Esdonk[1,2] | Naomi B. Klarenbeek[1] | Tomasz Cholewinski[1] | Tessa Nelemans[1] | Melloney J. Dröge[3] | Adam F. Cohen[1] | Rob G.J.A. Zuiker[1]

[1] Centre for Human Drug Research, Leiden, the Netherlands

[2] Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands

[3] Ardena Bioanalytical Laboratory BV, Assen, the Netherlands

Correspondence
Matthijs D. Kruizinga, Centre for Human Drug Research, Zernikedreef 8, 2333CL, Leiden, the Netherlands.
Email: mkruizinga@chdr.nl

Concentrations of drugs acting in the lungs are difficult to measure, resulting in relatively unknown local pharmacokinetics. The aim of this study is to assess the potential of exhaled breath condensate (EBC) as a matrix for pharmacokinetic analysis of inhaled and intravenous medication. A 4-way crossover study was conducted in 12 volunteers with tobramycin and salbutamol intravenously and via inhalation. EBC and plasma samples were collected postdose and analysed for drug concentrations. Sample dilution, calculated using urea concentrations, was used to estimate the epithelial lining fluid concentration. Salbutamol and tobramycin were largely undetectable in EBC after intravenous administration and were detectable after inhaled administration in all subjects in 50.8 and 51.5% of EBC samples, respectively. Correction of EBC concentrations for sample dilution did not explain the high variability. This high variability of EBC drug concentrations seems to preclude EBC as a matrix for pharmacokinetic analysis of tobramycin and salbutamol.

KEYWORDS

exhaled breath condensate, lung, pharmacokinetics, salbutamol, tobramycin

1 | INTRODUCTION

Pharmacological activity is usually derived from the time course of plasma concentrations and pharmacodynamic endpoints.[1] For pulmonary drugs, information about local concentrations could potentially improve pharmacokinetic analysis, since pharmacological activity depends on adequate drug levels at the effect site.[2] Lung penetration studies rely on bronchoalveolar lavage or sputum induction techniques for the measurement of drugs in the epithelial lining fluid (ELF) of the lung.[3,4] Bronchoalveolar lavage is invasive and potentially risky, which

Abbreviations: AUC, Area under the curve; CV, Coefficient of variation; EBC, Exhaled breath condensate; ELF, Epithelial lining fluid; LLOQ, Lower limit of quantification

The authors confirm that the Principal Investigator for this paper is Rob G.J.A. Zuiker and that he had direct clinical responsibility for volunteers

discourages use in vulnerable patients, children and healthy subjects. Therefore, new sampling matrices are needed. A matrix of interest is exhaled breath condensate (EBC).[5]

EBC is obtained by cooling exhaled breath through contact with a cold condenser. Samples are collected as fluid or frozen material and represent the ELF, diluted in condensed water from inhaled air and some saliva.[6-8] EBC application for biomarker quantification has been limited by poor reproducibility and high variability.[9] Several solutions have been proposed to improve reliability of EBC, such as to control for sample dilution factor obtained via EBC urea concentrations.[10-12]

Drug concentrations have already been measured in exhaled breath following administration of several drugs.[13-18] Nonetheless, no studies have assessed EBC concentrations after inhaled administration or reported proper concentration–time curves of EBC. The aim of this study is to assess the potential of EBC as a matrix for pharmacokinetic analysis of 2 common respiratory drugs: **salbutamol** and tobramycin.

What is already known about this subject

- Knowledge of drug concentration in lung tissue could aid in the development of pharmacokinetic models of drugs acting in the lung.
- Exhaled breath condensate is a noninvasive sampling matrix for the epithelial lining fluid of the lung.
- Several drugs have already been detected in single exhaled breath condensate samples.

What this study adds

- Measurable salbutamol and tobramycin concentrations are present in serial exhaled breath condensate samples after inhaled administration.
- Variability appears to be high and hampers reliable pharmacokinetic analysis.
- Using exhaled breath condensate urea concentration to correct for dilution in serial samples does not improve variability.

2 | MATERIALS AND METHODS

This study was conducted at the Centre of Human Drug Research in Leiden, the Netherlands from January to November 2018. The study protocol was reviewed and approved by the Beoordeling Ethiek Biomedisch Onderzoek Foundation Review Board (Assen, the Netherlands) prior to initiation of the study. The study was conducted according to the Dutch Act on Medical Research Involving Human Subjects and in compliance with good clinical practice. Twelve healthy, nonsmoking male subjects aged 18–65 years and body mass index between 18 and 35 kg/m^2 were included in this study. Subjects with a history or evidence of lung disease were excluded from this study.

2.1 | Study design

This was an open-label, 4-way crossover study. Visits were planned with a washout period of 3–7 days. Salbutamol and tobramycin were determined suitable medication to use in this proof-of-concept study, because they are commonly used, are available for intravenous use and inhalation, and have ample data available regarding plasma pharmacokinetics. Subjects were administered 1 mg/kg tobramycin intravenous (Obracin diluted in 50–100 mL 0.9% NaCl) over 30 min, 250 or 500 μg salbutamol by intravenous infusion (Ventolin Injection 0.5 mg/mL) over 2–8 min, 170 mg tobramycin (Vantobra) by inhalation using a Medix AC2000 nebulizer (Clement Clarke International) or 400 μg salbutamol (Ventolin Evohaler, GSK, London, UK) by inhalation with a spacer device (Volumatic).

Paired EBC and plasma samples were collected at 2 (salbutamol) or −15 and 5 (tobramycin) min pre-dose and at 10, 20, 40, 60, 80, 120, 180, 240, 300 and 420 min postdose. Additional plasma and EBC samples were collected from 8 subjects at 600 and 720 min dose after inhaled administration.

2.2 | Sample collection and analysis

EBC was collected according to European Respiratory Society guidelines during 5 min of tidal breathing using the Ecoscreen (Jaeger, Hoechberg, Germany).[19] EBC samples were stored at −80°C until further analysis. A liquid chromatography–tandem mass spectrometry assay was developed by Ardena Bioanalytical Laboratory to quantify tobramycin and salbutamol in plasma and EBC, and urea in EBC (Supplementary Text 1). Urea concentrations were measured as a marker for dilution. At the start of each study day, plasma urea concentration was determined. Dilution factor was calculated (D_{EBC} = $[urea]^{plasma}$/$[urea]^{EBC}$) and was multiplied with EBC tobramycin or salbutamol concentration to get a dilution-corrected EBC concentration. The coefficient of variation (CV) was calculated per time point until 180 min postdose and compared to the CV before correction.

2.3 | Statistics and pharmacokinetic analysis

As this was an exploratory study, no formal power analysis was performed. Pharmacokinetic endpoints were summarized descriptively. When tobramycin or salbutamol was undetectable, 50% of the lowest estimated concentration was imputed for graphical and statistical purposes. Descriptive analysis was performed using SPSS Version 25 (IBM, Armonk, NY, USA). Pharmacokinetic parameters were calculated using R version 3.5.2.[20] The area under the curve (AUC) was calculated as $AUC_{0\text{-last}}$ for EBC parameters and extrapolated to infinity (AUC_{inf}) for plasma parameters using the terminal elimination rate constant, determined by the log-linear regression of the last observations above the lower limit of quantification (LLOQ). The bioavailability (F)

was calculated on an individual level and summarized descriptively. When insufficient data were available for the log-linear regression, the AUC_{inf} was not included in the results and the mean AUC_{inf} was imputed for the calculation of the bioavailability (F). The clearance and volume of distribution were calculated and corrected for by an individual's F. Promasys software (OmniComm, Fort Lauderdale, FL, USA) was used for data management.

3 | RESULTS

3.1 | Subjects, safety and tolerability

Twelve healthy male volunteers were included, and all subjects completed the 4 study days. Baseline characteristics are shown in Table 1. Twelve subjects received 1 mg/kg tobramycin by intravenous infusion, 250 μg (3 subjects) or 500 μg (9 subjects) salbutamol by intravenous infusion, 170 mg tobramycin by inhalation and 400 μg salbutamol by inhalation.

3.2 | Pharmacokinetics

Mean (± SD) plasma and EBC concentration–time curves of all subjects after intravenous and inhaled administration of tobramycin and salbutamol are shown in Figure 1. Pharmacokinetic parameters are summarized in Table 2. Individual concentration–time curves can be found in Supplementary Figure S1 and S2. One subject had an unexplained increase >2 SD in salbutamol concentration in 1 plasma sample 2 hours after intravenous infusion, which was excluded during the analysis. After intravenous administration, tobramycin concentrations were undetectable in EBC and a quantifiable concentration of salbutamol was found in only 3 EBC samples (2.5%). However, measurable concentrations of tobramycin and salbutamol after inhaled administration were present in EBC samples of all subjects. Salbutamol was undetectable in 75% of subjects after 120 min. The proportion of samples with a quantifiable concentration of salbutamol per time point ranged from 8–92% (Supplementary Figure S3).

TABLE 1 Baseline characteristics of participants

Demographic	Value
Male, *n* (%)	12 (100)
Age (y)	24.6 (6.8)
BMI (kg/m)	22.5 (2.6)
Height (cm)	184 (10.1)
Weight (kg)	75.8 (11.4)
Race, *n* (%)	
• white	11 (91.7)
• Asian	1 (8.3)

Data are presented as mean (standard deviation) unless stated otherwise. All participants completed the 4 treatment days. BMI, body mass index.

3.3 | Urea and dilution

Urea concentration was measured in all EBC samples with a quantifiable drug concentration. Individual urea concentrations and D_{EBC} estimates are displayed in Supplementary Figure S4. Mean D_{EBC} was 531 (range 32–5719). Concentration–time curves of the estimated ELF drug concentration are displayed in Figure 1. The mean coefficient of variation (CV) per time point after correction for dilution was 144% (SD 40%) for salbutamol, compared to 124% (SD 28%) before correction. Mean CV of tobramycin concentration after correction was 129% (SD 32%), compared to a prior 114% (SD 24%).

4 | DISCUSSION

In this study, the potential of EBC as a matrix for pharmacokinetic analysis of drugs acting in the lungs was investigated. A 4-way crossover study was conducted wherein we obtained serial paired plasma and EBC samples after intravenous and inhaled administration of tobramycin and salbutamol.

The plasma pharmacokinetics after administration of intravenous and inhaled salbutamol and tobramycin were determined. Calculated pharmacokinetic parameters of salbutamol in plasma corresponded with results reported in other studies regarding maximum plasma concentration (C_{MAX}), time to C_{MAX} and half-life.[21,22] Plasma C_{MAX} of inhaled tobramycin was lower than expected, which may be a result of the chosen administration technique.[23]

We are the first to report serial EBC drug concentrations. We were unable to measure salbutamol and tobramycin in EBC after intravenous administration of salbutamol and tobramycin in 97.5 and 100% of the samples, respectively. Low concentrations were expected in the case of tobramycin, considering the fact that tobramycin is a large (molecular weight 467.52 g/mol), polarized molecule and therefore does not easily pass barriers. This is illustrated by the poor bioavailability of inhaled tobramycin. However, we expected salbutamol to be detectable in more samples, considering that salbutamol is a smaller molecule (molecular weight 239.32 g/mol) and the fact that several researchers have demonstrated the ability to detect intravenously or orally administered drugs with similar properties in exhaled breath or EBC.[13-16] We assume that salbutamol plasma concentrations were insufficient after administration in order to achieve EBC salbutamol concentrations larger than the LLOQ, even with the high intravenous dose of 500 μg. This hypothesis should be confirmed with a more sensitive assay with a lower LLOQ.

Salbutamol and tobramycin were detected in EBC after inhalation of 400 μg salbutamol and 170 mg of tobramycin. Mean salbutamol concentrations in EBC after inhaled administration decreased below the LLOQ after approximately 2 h, which is about 50% of the amount of time salbutamol is believed to have an effect on pulmonary function.[24] The highest EBC salbutamol concentrations were present during the absorption phase of salbutamol in plasma after inhaled administration. This indicates that higher EBC concentrations are detected when there is active exchange of salbutamol between the

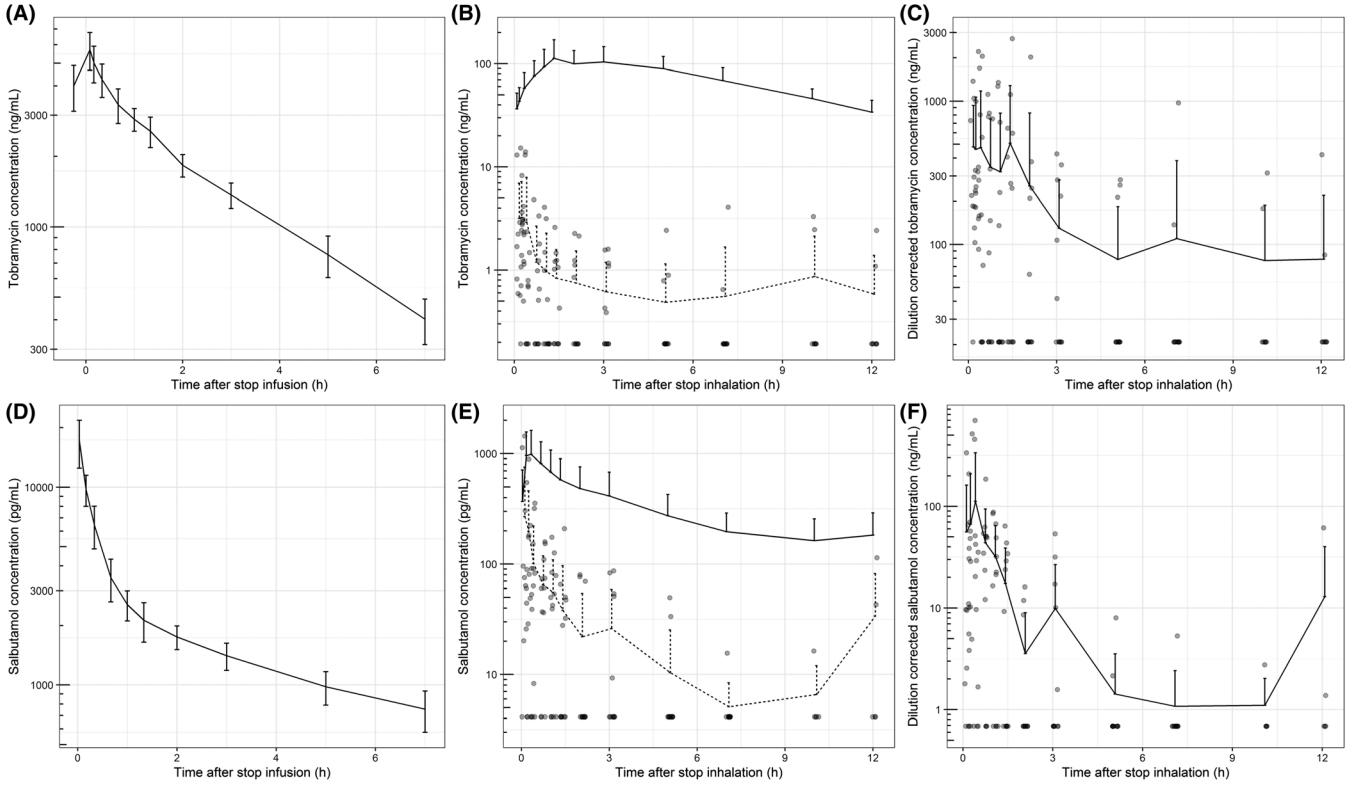

FIGURE 1 Plasma and exhaled breath condensate (EBC) concentration–time curves after intravenous administration of tobramycin and salbutamol. (A) Concentration–time curve of mean tobramycin concentration in plasma (± standard deviation, SD) after intravenous administration of 1 mg/kg tobramycin (n = 12); (B) concentration–time (mean + SD) curve of plasma (solid line) and EBC (dotted line) tobramycin concentration after inhalation of 170 mg tobramycin; (C) concentration–time curve of mean (SD) EBC tobramycin concentration after inhaled administration of 170 mg tobramycin, corrected for sample dilution; (D) concentration–time curve of mean salbutamol concentration in plasma (±SD) after intravenous administration of 500 μg salbutamol (n = 9); (E) concentration–time (mean + SD) curve of plasma (solid line) and EBC (dotted line) tobramycin concentration after inhalation of 400 μg salbutamol; (F) concentration–time curve of mean (SD) EBC salbutamol concentration after inhaled administration of 400 μg salbutamol, corrected for sample dilution; sample concentrations lower than the lower limit of quantification were estimated when possible or fixed on 50% of the lowest concentration. Dots represent individual measurements

inhaled air, ELF and plasma. However, variability in EBC was high as shown in the supplementary individual plots.

Mean EBC tobramycin concentration decreased sharply in the first hour, which correlated with the duration of the absorption phase in plasma. After the first hour, tobramycin concentrations remained stable or below the LLOQ. This may correspond with the relatively long half-life (4.2 h) of tobramycin in plasma after inhaled administration compared to the half-life after intravenous administration (2.3 h). It is possible that ELF acts as a tobramycin reservoir enabling flip-flop kinetics, with tobramycin gradually diffusing towards the systemic circulation. This causes a longer elimination phase, while tobramycin also remains detectable in the diluted ELF that is EBC.

After all, EBC reflects a dilution of the ELF.[8,19] Variation in dilution factors of EBC samples has been a frequently hypothesized cause of variability. Urea has been proposed as marker for dilution in EBC.[12,25] We measured urea concentrations in EBC and calculated the estimated dilution. Mean D_{EBC} was slightly lower than reported in other studies[10,25,26] and varied greatly between and within subjects (Supplementary Figure S4), providing an explanation for the observed variability. The CV increased after correction, which did not meet our hypothesis regarding reduced variability.

EBC research in general has been plagued by high variability within and between subjects.[9,19,27] While several authors have reported methods to reduce variability,[10-12,25] this too is poorly reproducible and has not resulted in the development of clear guidelines with standardized methods.[19] Consequently, EBC has not yet reached clinical practice. The fact that 2 commonly used respiratory drugs could not be detected in EBC for the majority of samples postinhalation appears to disqualify EBC as a matrix for pharmacokinetic analysis.

This study has limitations. Variation in inhalation technique could explain the lower than expected plasma concentrations of tobramycin, but also the variability in measured EBC concentrations.[28] In addition, although the EBC device contains a saliva trap, it cannot not be excluded that samples taken directly after administration represent oropharyngeal salbutamol deposition rather than lung pharmacokinetics. Furthermore, almost all sample concentrations were below or on the lower end of the calibration curve. Variability may therefore also result from assay variability as opposed to biological or device variability.[7] Finally, the method to use estimated sample concentrations below the LLOQ, as well as impute 50% of the lowest concentration when no estimation was possible, is a debated subject.[29] Nevertheless, the use of other methods would not change the main outcome

TABLE 2 Pharmacokinetic parameters mean (standard deviation) [range]

	Parameter	Tobramycin intravenous (1 mg/kg)[a]	Tobramycin inhalation (170 mg)	Salbutamol intravenous (500 µg)	Salbutamol inhalation (400 µg)
Plasma	t_{MAX} (h)	0.09 (0.02) [0.08–0.17]	2.72 (1.9) [1.33–7.0]	0.04 (0.02) [0.03–0.10]	0.31 (0.14) [0.17–0.69]
	C_{MAX} (ng/mL/pg/mL)[b]	5753.3 (1055.2) [4030–7090]	123.2 (55.7) [50.5–247]	17133.3 (4637.1) [10 600–248 000]	1012.5 (615.1) [486–2600]
	AUC_{inf} (ng*h/mL/pg*h/mL)	14 232.8 (1682.8) [11 736.2–17 036.2]	1090.34 (389.1) [337.7–1715.4]*	19 274.4 (4593.0) [13 511–26 835]	4128.7 (2487.8) [1588.3–10 842.9]
	$t_{½}$ (h)	2.23 (0.25) [1.72–2.68]	4.2 (0.63) [3.09–5.08]*	4.43 (0.87) [3.64–5.96]	4.04 (1.15) [2.04–5.89]
	Volume of distribution (L)	17.26 (3.28) [12.23–22.76]	31.1 (4.0) [25.8–36.5]*	168.4 (22.5) [134.12–194.78]	143.4 (57.6) [70.6–262.5]
	Clearance (L/h)	5.39 (0.99) [3.83–6.88]	5.2 (1.0) [3.8–6.9]*	27.23 (6.25) [18.63–37.01]	25.22 (7.75) [8.3–37.01]
	F (%)	-	3.4 (1.1) [1.4–5.5]	-	22.5 (8.5) [10.7–40.6][c]
EBC	EBC samples > LLOQ (%)	0	51.5	2.5	50.8
	EBC $AUC_{0\text{-last}}$ (ng*h/mL/pg*h/mL)	-	8.39 (5.1) [2.39–16.98]	-	260.3 (224.9) [32.2–645.0]
	EBC C_{MAX} (ng/mL/pg/mL)[a]	-	5.23 (4.78) [0.7–15.2]	-	336.25 (468.74) [25.9–1440]
	EBC t_{MAX} (h)	-	2.60 (4.0) [0.17–10.1]	-	1.36 (3.39) [0.12–12.1]
	CV[d] Before correction for D_{EBC}	-	114 (24)	-	124 (28)
	After correction for D_{EBC}	-	129 (32)	-	144 (40)

[a]Mean dose: 75 mg;

[b]Salbutamol concentrations are reported as pg/mL, tobramycin concentrations are reported as ng/mL;

[c]Calculated on $n = 9$;

[d]Mean coefficient of variation calculated for all time points until 180 min postdose.AUC, area under the curve; EBC, exhaled breath condensate; F, bioavailability; D, dilution; C_{MAX}, maximum plasma concentration; t_{MAX}, time to C_{MAX}; LLOQ, lower limit of quantification

of this study. A main strength of this study is the longitudinal analysis of EBC concentration and EBC dilution. The 4-way crossover design allowed for the calculation of the bioavailability of tobramycin and salbutamol on an individual level. Finally, EBC collection was conducted in a standardized manner in line with European Respiratory Society guidelines.[19]

5 | CONCLUSION

In conclusion, salbutamol and tobramycin can be quantified in EBC after inhaled administration, especially during the plasma absorption phase, but not after intravenous administration. The high amount of variability of EBC drug concentrations seems to preclude its use for robust pharmacokinetic analysis and as such, we do not recommend its use in this area.

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CONTRIBUTORS

M.K. conducted the study, analysed the results and wrote the manuscript, W.B. conducted the study and reviewed the manuscript, T.N. and T.C. performed most measurements and reviewed the manuscript, M.v.E. designed the study, performed the PK analysis, wrote the manuscript, M.D. developed the analytical assay, analysed the samples and reviewed the manuscript, N.K., A.C. and R.Z. designed the study, supervised study conduct and wrote the manuscript.

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

DATA SHARING

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Matthijs D. Kruizinga https://orcid.org/0000-0002-2054-2187
Willem A.J. Birkhoff https://orcid.org/0000-0001-5832-0646
Michiel J. van Esdonk https://orcid.org/0000-0001-8159-0273
Adam F. Cohen https://orcid.org/0000-0001-7452-6222
Rob G.J.A. Zuiker https://orcid.org/0000-0001-5604-0157

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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