Comment on: Pharmacokinetics of inhaled colistin in patients with cystic fibrosis

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Sir,

Ratjen et al.1 recently published an important paper in JAC reporting the pharmacokinetics of colistin after inhalation of colistin methanesulphonate in patients with cystic fibrosis (CF). HPLC was used to measure the concentrations of the formed colistin. The paper raises a number of important issues that deserve comment.

It is important not to use the terms colistin and colistin methanesulphonate (sodium salt, or colistimethate-Na in the paper1) interchangeably. The chemistry, pharmacokinetics, pharmacodynamics and toxicity of these two entities are substantially different.2–5 Most importantly, colistin is formed from colistin methanesulphonate both in vitro6 and in vivo.7,8 Even though some manufacturers (such as Grünenthal, Germany) label the content of injection vials of colistin methanesulphonate with ‘158 mg colistin methanesulphonate is equal to 66 mg colistin’, this labelling is misleading because it is based on antibacterial activity measured with microbiological assays and does not mean that there is 66 mg of colistin in each vial. Therefore, we strongly recommend that any pharmacokinetic calculations on colistin or colistin methanesulphonate should not be based on ‘66 mg colistin’.

The HPLC assay used by Ratjen et al.1 was very similar to the one reported previously from another laboratory9 using derivatization with 9-fluorenylmethyl chloroformate on solid-phase extraction C18 cartridges; in the previously reported HPLC assay,10 colistin sulphate was employed to prepare calibration curves for measurement of colistin (base) in biological fluids. In the paper of Ratjen et al.,1 it is not clear whether colistin sulphate, colistin A or colistin methanesulphonate (sodium) was used for the calibration curves of the HPLC assay. Ratjen et al.1 reported the amount (0.18–16.13 mg) of ‘colistin methate’ recovered in urine was equal to a mean 4.3 ± 1.5% (range 0.3–24.2%) of the inhaled dose. Unfortunately, it is not clear how the concentrations of ‘colistin methate’ in urine were measured. It appears that the urinary recovery was calculated based on the recovered amount of colistin (base) and the dose of ‘66 mg colistin’.

Considering the hydrolysis of colistin methanesulphonate to colistin in vivo4,7,8 and in vitro6, such calculation of urinary recovery using the dose of ‘66 mg colistin’1 is inappropriate. In addition, it is unclear whether the authors1 have allowed for the molecular weight difference between colistin methanesulphonate (sodium, average molecular weight 1743), colistin sulphate (average molecular weight 1403, if they used it for calibration curves for colistin) and colistin (average molecular weight 1163)7 when the concentrations of ‘colistin’ were calculated.

Ratjen et al.1 used the HPLC peak for polymyxin E1 to generate calibration curves for colistin concentrations. Usually, the two major components of colistin, colistin A (polymyxin E1) and colistin B (polymyxin E2), account for more than 85% of colistin,10 but the ratio of these two components may vary substantially between 3:1 and 1:1.9,10 It is not clear how the authors1 calculated the concentrations of polymyxin E1 in the HPLC assay as the commercially available colistin sulphate is a mixture of many components.9,10 In addition, we are not aware of any literature indicating that polymyxin E2 has no antibacterial activity; hence, the claim by Ratjen et al.1 that ‘colistin is a pro-drug that is converted into its active component polymyxin E1’ is questionable. Indeed, polymyxin E1 is one of the constituents of colistin.

It should be noted that the clearance of colistin reported by Ratjen et al.1 should be regarded as an apparent clearance because the amount of the inhaled dose of colistin methanesulphonate reaching the systemic circulation in the form of colistin is unknown.

In summary, Ratjen et al.1 provided some potentially useful information on the pharmacokinetics of colistin after inhalation of colistin methanesulphonate. However, because of lack of clarity regarding the quantification of colistin in biological fluids and the pharmacokinetic analysis, caution is required when these data are used as reference for inhalation therapy of colistin methanesulphonate in CF patients.

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Transparency declarations

We do not have any financial, commercial or proprietary interest in any drug, device or equipment mentioned in this piece of correspondence.

References

4. Li J, Milne RW, Nation RL et al. Pharmacokinetics of colistin methanesulphonate and colistin in rats following an intravenous dose.


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Pharmacokinetics of inhaled colistin in patients with cystic fibrosis: authors’ response
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Sir,

We thank Li and Nation1 for their thoughtful comments on our study on pharmacokinetics of inhaled colistin in cystic fibrosis (CF) patients.2 It is well taken that colistin contains a varying mixture of ingredients including polymyxin E1, E2 and E3. We are not aware of any data that polymyxin E2 and E3 have antimicrobial activity, but their pharmacokinetic profile may differ from that of polymyxin E1. As our interest was focused on the antimicrobial activity of colistin, we have used the term colistin and colistin methanesulphonate interchangeably. We agree with Li and Nation that using the term colistin methanesulphonate may be the more appropriate terminology. However, since the other components of colistin have no established antimicrobial effect, this bears no direct practical relevance for treatment with inhaled colistin in CF patients where the antimicrobial activity is of primary relevance.

The comment that polymyxin E1 and E2 contents may vary between different charges of the drug is well taken and also applies for the product used in this study. For treatment of the patients a batch with a known polymyxin composition containing 73% polymyxin E1 was used. Taking this composition into account the concentration of ‘total’ colistin was estimated. It is agreed that the precision of these calculations is limited due to the fact that during formation of colistin from colistin methanesulphonate a variety of different intermediates appear. At the time of sampling the composition thereof is not known.

For the calibration curves of the HPLC assay Colistin sulphate European Pharmacopoeia standard (Colistin sulfate CRS batch2) was used. A molecular weight correction was performed to calculate the polymyxin E1 concentration.

It is agreed that, for the sake of clarity, the clearance should be addressed as relative clearance. The term ‘apparent’ clearance was not used to prevent confusion with the term apparent volume of distribution.

Transparency declarations
No declarations were made by the authors of this paper.

References

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Activity of mecillinam against AmpC ß-lactamase-producing Escherichia coli
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Sir,

We read with interest the recently published correspondence of Thomas et al.1 which looked at the activity of mecillinam against extended spectrum ß-lactamase (ESBL)-producing Escherichia coli and Klebsiella spp. The authors demonstrated significantly raised mecillinam MICs for ESBL producers when tested at higher inocula (10^6 cfu/spot). In addition to ESBLs, other enzymes, such as AmpC ß-lactamas, are also emerging as important resistance mechanisms in Klebsiella pneumoniae and E. coli.