Tobramycin dosing in adults with cystic fibrosis: balancing safety, efficacy and tolerability

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Background

Intravenous (IV) tobramycin is a key component in the antibiotic treatment of pulmonary exacerbations in cystic fibrosis (CF) patients colonised with Pseudomonas aeruginosa (PsA) (1-3). Therapeutic tobramycin monitoring is essential to prevent toxicities, however, repeated blood sampling is onerous to patients. Recommendations for tobramycin dosing of 10mg/kg/day aim for peak concentrations (C_{max}) of 20 – 40mg/L, area-under-the-curve at 24 hours (AUC_{24}) of 70–100mg.h/L and a trough concentration (C_{trough}) of <0.5mg/L (3,4). The Prince Charles Hospital Adult CF Centre (TPCH ACFC) employs a conservative tobramycin dosing strategy of 5 – 7mg/kg/day to prevent long term toxicity (3-5), however this may result in suboptimal tobramycin exposure.

Aim

i) Assess frequency of "sub-therapeutic" tobramycin levels, based on C_{max} and AUC achieved in subjects receiving IV tobramycin with current TPCH ACFC dosing strategies, and;

ii) Validate finger-prick capillary blood sampling as a minimally invasive approach to tobramycin blood level monitoring.

Methods

Matched venous and capillary blood samples were collected from CF patients treated with IV tobramycin for an acute pulmonary exacerbation on Day 7 of treatment 0.5–4 hours and 6–14 hours following IV tobramycin administration. C_{max} and AUC were calculated by the linear regression model adapted from Begg et al(6). Bland-Altman analysis was used to determine agreement between venous and capillary blood sampling.

Results

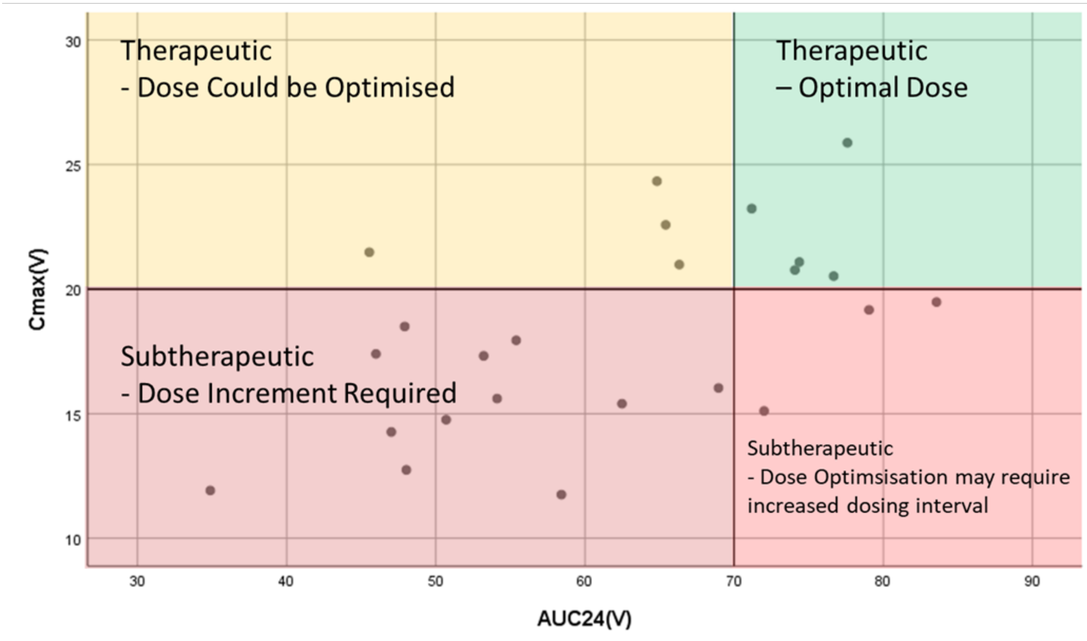
Forty-nine treatment episodes in 40 participants were assessed. The table below outlines participant characteristics and tobramycin dosing regimens.

Table: Participant Characteristics (N=40)

Gender	Male = 29 (72.5%) Female = 11 (27.5%)
Mean Age	34 years
Mean BMI	22
Mean length of stay	14 days
Mean FEV1% predicted at baseline	44%
Mean tobramycin dose (mg/kg)	5mg/kg
Tobramycin dosing frequency 24 hourly 36 hourly 48 hourly	 22 (55%) 15 (27.5%) 3 (7.5%)

The graph below shows the calculated C_{max} and AUC_{24} in the 24 treatment episodes where participants received tobramycin 24 hourly compared to the minimum target C_{max} (20 mg/L) and AUC_{24} (70mg.hr/L) values for tobramycin defined in the literature (3,4). In 21/49 (43%) episodes C_{max} was sub-therapeutic (<20mg/L). In 16/21 (76%) of these episodes AUC_{24} was also sub-optimal (<70-100mg.h/L).

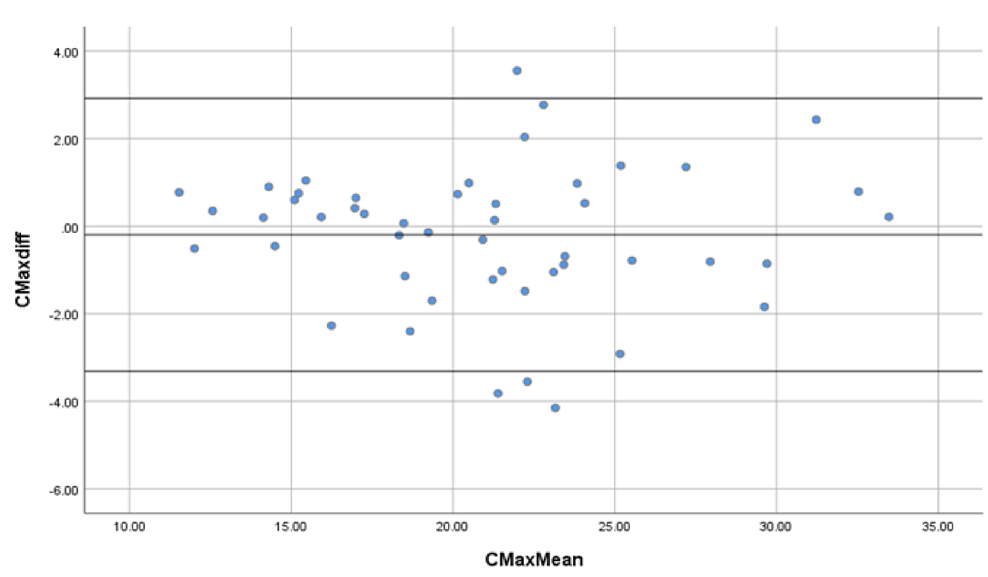
C_{max} versus AUC_{24} of patients on 24hour Dosing



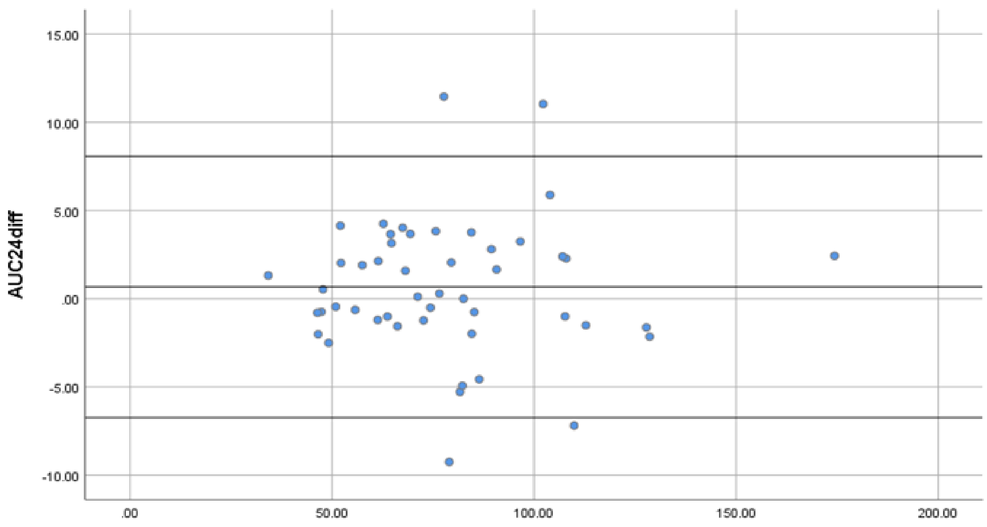
Thirty-six hourly dosing was utilised in 22 treatment episodes. In six of these episodes C_{max} and AUC_{36} were sub-therapeutic (<20mg/L and <105-150mg.h/L respectively). C_{max} was 20 – 40mg/L in each subject who received 48 hourly dosing. C_{trough} was <0.5mg/L in all 49 treatment episodes. The C_{max} , AUC and C_{trough} were acceptable based on dosing interval in 17/49 (35%) of all treatment episodes. Bland-Altman plots and correlation analyses (below) showed high levels of agreement between venous and capillary tobramycin concentrations.

Bland-Altman Plot Agreement between:†

i) Venous and Capillary blood C_{max}



ii) Venous and Capillary blood AUC_{24}



†One-sided T-tests and linear regression excluded significant differences and proportional bias between venous and capillary testing for AUC_{24} and C_{max}.

Conclusion

Tobramycin dosing was considered sub-therapeutic in 32/49 (65%) of treatment episodes. High levels of agreement between finger-prick and venous sampling techniques supports the utility of minimally invasive serum tobramycin concentration monitoring. Our results demonstrate that TPCH ACFC tobramycin dosing strategies are conservative compared to current recommendations. Finger-prick capillary blood sampling offers a less invasive alternative to venous sampling for tobramycin concentration monitoring in adult CF patients.

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