Abstract

Individuals respond differently to medication as a result of their genetic inheritance. These differences can result in the under- or over-dosing of medication, which may affect the efficacy or in the case of aminoglycosides (kanamycin) and polypeptides (capreomycin), result in toxicity. In South Africa, administration of the standardised Drug Resistant - Tuberculosis (DR-TB) medication regimen is simplified across four weight bands. These bands accommodate the formulations available in the country while complying with international requirements for minimum, maximum and average dose per kilogram. There is a dearth of information on the ideal concentration, pharmacokinetics, and pharmacodynamics of kanamycin (KM) and capreomycin (CM) in patients with DR-TB and relationship of this on hearing levels. Thus, this study aimed to establish the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels.

This feasibility study employed a prospective, cross-sectional, exploratory, descriptive and case series research design. A total of 22 participants (mean age 33.78 years, ±7.3) participated in this multi-site study at Helen Joseph (HJH) and South Rand Hospitals (SRH). The majority of the paryicpants were females (68%, *n*=15). Participants underwent audiological (otoscopy, tympanometry, ultra high frequency DPOAEs, ultra high frequency pure tone audiometry) and pharmacological assessments at baseline and every two weeks for the first three months of treatment. Creatinine clearance was measured, and the overall outcome of treatment was evaluated in relation to the pharmacokinetics.

Results revealed high-frequency hearing loss with both kanamycin and capreomycin, specifically in the ultra-high frequencies (9kHz to 16kHz). Clinically significant ultra-high frequency loss noted was with pure tone audiometry from week four after the initiation of

treatment, and from week six in the high frequencies (6kHz to 8kHz). Pharmacokinetic measurements showed erratic levels of kanamycin and capreomycin, with considerable differences among individuals, specifically with the peak readings. Mean peak levels for kanamycin were within the target range yet were subtherapeutic for the capreomycin participants. Kanamycin also correlated to more reduced kidney function when compared to capreomycin. Participants' culture converted within the first two months from baseline, however, long-term culture results are unknown. Trough levels were also below 10 μg/ml and not within a toxic range, despite the hearing loss detected.

This research identified many challenges with regard to establishing the feasibility of investigating the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin in patients with DR-TB and the relationship between hearing levels. Participant enrolment was poor, with high attrition. This study also highlighted the need for a standardised ototoxicity monitoring protocol designed for this population which led to the development of 'Ototcalc': an ototoxicity calculator in the form of a mobile application designed to assist healthcare professionals in the classification of significant ototoxicity as well as with management recommendations. With the considerations identified in this study to further enhance the feasibility, the pharmacokinetics and pharmacodynamics of kanamycin and capreomycin are recommended for further exploration in relation to toxicity and efficacy with a larger sample, combined with the use of 'Otocalc'.

Keywords: Drug Resistant-Tuberculosis, Ototoxicity, Pharmacokinetics, Pharmacodynamics, Kanamycin, Capreomycin, Otocalc