Assessment of Ototoxicity in Aerosolized Amikacin Therapy for Refractory Nontuberculous Mycobacterial Lung Disease

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Introduction

Nontuberculous mycobacterial lung disease (NTM-LD) is a progressive chronic condition caused by various species of NTM. The global prevalence and impact of NTM-LD are on the rise. Current therapeutic guidelines recommend long-term, multidrug therapy and the incorporation of injectable aminoglycoside antibiotics like amikacin (AMK) alongside standard oral regimens, particularly in patients with cavitary or extensive lung involvement caused by *Mycobacterium avium complex* (MAC) or *M. abscessus complex* (MABC). Nonetheless, the sustained systemic administration of AMK is often curtailed by severe adverse effects, notably auditory or renal toxicity. Consequently, recent attention has shifted towards aerosolized antibiotics inhalation therapy to enhance pulmonary drug delivery while minimizing systemic complications. This study aims to assess the ototoxic effects of AMK inhalation therapy for NTM-LD.

Materials and Methods

The study enrolled 48 patients aged 50 to 89 years (mean, 67.9±10.3 years) who commenced AMK inhalation therapy for refractory NTM-LD caused by MABC or MAC at Samsung Changwon Hospital from March 2019 to February 2023. All patients met the diagnostic criteria for NTM-LD and had no prior exposure to AMK inhalation therapy. The addition of AMK inhalation therapy was adjunctive to each patient's existing treatment regimen. Commercially available intravenous amikacin sulfate (500mg/2ml) was diluted with 2ml of saline and placed in a compressor nebulizer for inhalation. The initial treatment protocol of AMK inhalation was 500mg three times weekly. Patients were followed up at 1, 3 and 6 months after the initiation of AMK inhalation therapy. Ototoxicity was defined based on established criteria: a hearing loss of at least 10 dB at two or more consecutive frequencies, a hearing loss of at least 20dB at a single isolated frequency, or the absence of response at any of three consecutive frequencies on a post-treatment audiogram compared with that on the baseline audiogram in either ear at any frequency (250, 500, 1,000, 2,000, 4,000, or 8,000 Hz).

Results

Baseline audiometry at the time of inhaled amikacin initiation was available in all patients: seven patients (14.6%) had normal hearing sensitivity; sixteen (33.3%) had mild high frequency sensorineural hearing loss; twenty (41.7%) had mild to moderate sensorineural hearing loss and five (10.4%) had moderate to severe sensorineural hearing loss. During the 6-month follow-up period, ototoxicity was observed in 10 patients (21%). Changes in hearing loss occurred in 3 patients from the normal hearing group, 5 from the mild high frequency sensorineural hearing loss group, and 2 from the mild to moderate sensorineural hearing loss group, leading to a dose reduction or discontinuation of AMK inhalation therapy. Hearing loss was confirmed in 2 patients within 1 month, 7 patients at 3 months, and 1 patient at 6 months. After dose adjustments of discontinuation of AMK inhalation in patients experiencing ototoxicity, hearing threshold was restored.

Discussion

The goal of MTN-LD treatment is to improve symptoms and radiologic findings while achieving short periods of negative sputum. However, treatment of NTM-LD requires lengthy, and often toxic, antibiotic regimens, which may be unsuccessful. Aerosolized AMK was associated with fewer toxic side effects as compared with previous reports systemic AMK. The relatively limited side effects seen with inhaled AMK and its potential capacity to treat NTM-LD suggest it may be a useful adjunct in treatment refractory disease. But this study has several limitation. First, its retrospective observational nature has potential biases. In addition, this study is limited by the low number of patents who treated with inhaled AMK. A third limitation is that the medications administered, aside from inhaled AMK, varied among patients, and other factors such as azithromycin, which could affect hearing threshold changes, were not excluded. Finally, the long-term clinical responses and safety of three-times-weekly AMK inhalation therapy could not be fully evaluated because the follow-up duration was relatively short.

Conclusion

Currently, there is a lack of established guidelines regarding the optimal dosage of AMK in aerosolized AMK therapy for managing NTM-LD. Hence, given the prevalence of adverse effects, further investigation into the optimal dosage and dosing intervals for amikacin inhalation therapy is warranted.

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