Pharmacokinetics of Intravenous Amikacin in Intermittent Hemodialysis:

Two Cases of Peritoneal Dialysis Peritonitis caused by Nontuberculous Mycobacterium (NTM)

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INTRODUCTION & BACKGROUND

Aminoglycoside Dosing

- Pharmacokinetic (PK) literature in intermittent hemodialysis (iHD) is outdated - current practice employs more efficient iHD modalities.
- Efficacy is obtained by maximizing the peak serum concentration (C_{max}) to minimum inhibitory concentration (MIC) ratio.
- Toxicity (nephrotoxicity) is thought to be related to body exposure as measured by the area under the serum concentration versus time curve (AUC).

Nontuberculous mycobacterium (NTM)

- Amikacin is one of the most active parenteral agents against Gram-negative bacilli and NTM isolates, including multidrug resistant.
  - ATS/IDSA guidelines recommend targeting peak levels in the low-20 mg/L range[1].
  - Current amikacin dosing recommendations for iHD patients (3-5 mg/kg given 30-60 minutes at the end of iHD) is unlikely to obtain target peak levels for serious infections including NTM, and may even lead to relatively high AUCs and toxicity.

Optimizing Pharmacokinetic/Pharmacodynamic (PK/PD) Principles

- Augmented dosing strategies ("high-dose" or "once daily") emphasize optimizing PK/PD and show similar, or less nephrotoxicity.
  - Goal: to maximize efficacy and minimize toxicity
  - Renal dysfunction patients were excluded from these studies

Experts have suggested that the ideal time to administer aminoglycosides in iHD patients is before the start of each iHD session. However, high-dose pre-iHD aminoglycoside dosing is uncommon since literature (clinical, PK/PD) supporting this practice is lacking.

METHODS

Dosing: Amikacin 7mg/kg (rounded to nearest 50mg) was administered 4 hours before start of iHD; dissolved in 100 mL D5W or NS; infused over 30 mins

Hemodialysis: iHD filter used in both patients was Fx1000 Helixone (Fresenius Medical Care). Blood flow rate = 250-600 mL/min; Dialysate flow rate = 500 mL/min; Ultrafiltration coefficient (mL/h x mmHg) = 75

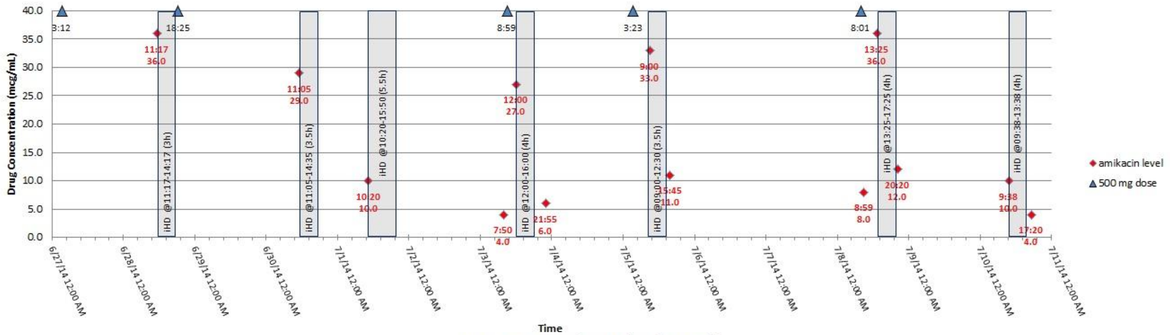
Therapeutic Drug Monitoring: amikacin levels were drawn as follows:

- pre-iHD (C_{max}, "peak")
- 4 hours post-iHD (C_{min1}, "post-iHD trough")
- pre-dose administration, pre-iHD (C_{min2}, "true trough")
- pharmacokinetic analysis assumed one compartment, linear kinetics

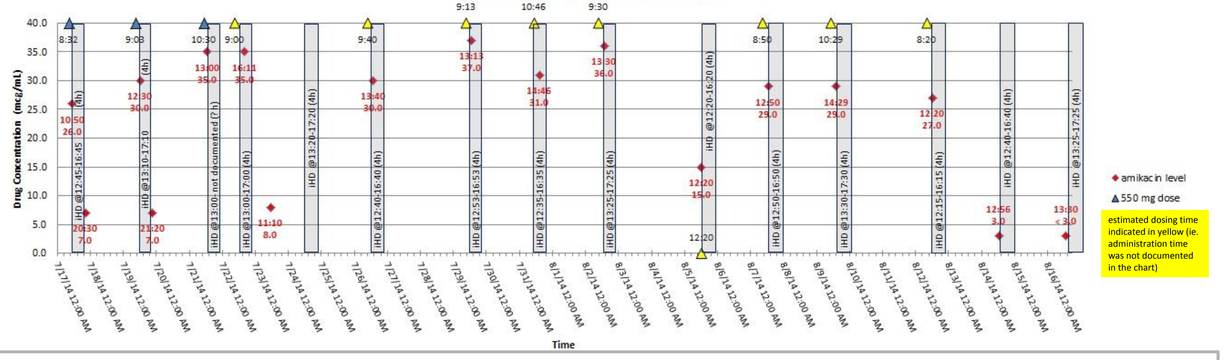
PURPOSE

We describe a high-dose strategy and pharmacokinetic monitoring for the use of intravenous amikacin in intermittent hemodialysis in two cases of peritoneal dialysis peritonitis caused by nontuberculosis mycobacteria (NTM), which required peritoneal dialysis catheter removal and conversion to intermittent hemodialysis (iHD).

Patient 1: amikacin level trend



Patient 2: amikacin level trend



CONCLUSION

- Administration of pre-iHD IV amikacin at 7mg/kg achieved guideline-recommended C_{max} levels in two cases of NTM peritonitis.
- Amikacin clearance with current iHD modalities was much more efficient than prior reports, while high-dose, pre-iHD dosing strategy successfully improved pharmacokinetic parameters (allowing high C_{max}, while decreasing overall amikacin exposure on non-iHD days).
- We suggest consideration of pre-iHD IV amikacin to optimize PK/PD for iHD patients who require high-dose therapy for serious infections.

References
1. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007 Feb 15;175(4):367-416.

Case report 1: *Mycobacterium fortuitum*

39 year old female with end stage renal disease (ESRD) secondary to IgA nephropathy on continuous cyclic peritoneal dialysis (CCPD) presented to clinic with 3 day history of discharge around the peritoneal dialysis (PD) exit site. The exit site and PD fluid were cultured and the patient was sent home with a prescription of cephalexin. The patient was changed to intraperitoneal vancomycin based on culture results (both showed gram positive bacilli). The patient was seen 8 days later with worsening peritonitis symptoms and admitted to the hospital.

Within 2 days of admission, a diagnosis of *M. fortuitum* peritonitis was made requiring PD catheter removal. On diagnosis, one dose of IV amikacin 500mg (7.25mg/kg) was administered, in conjunction with imipenem 500mg IV q12h and ciprofloxacin 500mg po daily. The patient had no residual renal function.

The day after PD catheter removal, iHD was initiated at 3x per week schedule and she was given a second dose of IV amikacin 500 mg following the first session of hemodialysis. Subsequent doses of IV amikacin were given pre-iHD to target pre-iHD levels (C_{max}) between 20-35 mg/L and trough target level <10 mg/L (C_{min1}). The patient reported tinnitis after 3 doses of pre-iHD amikacin. Despite normal audiometry testing, the decision was made to switch amikacin to cefoxitin to avoid potential adverse effects.

Case report 2: *Mycobacterium abscessus*

68 year old male with ESRD secondary to type 2 diabetes on CCPD was admitted with suspected PD peritonitis. He was initially prescribed intraperitoneal ceftazidime and cefazolin. Worsening symptoms led to PD catheter removal 6 days from initial presentation and the patient was transition to 3x weekly iHD. The following day, the patient was diagnosed with *M. abscessus* peritonitis and was prescribed cefoxitin 2g IV 3x/week post-iHD, amikacin 550mg (7mg/kg) IV 3x/week pre-iHD, and clarithromycin 500mg po daily. The patient had residual renal function of approximately 500 mL/day. The pre-iHD target level (C_{max}) was 20-35 mg/L and the trough target level <10 mg/L (C_{min1}). The patient continued on amikacin for a total of 27 days. No adverse effects related to amikacin were noted.

Microbiology Results

Table 1. *M. fortuitum* susceptibility report

Mycobacterium fortuitum	
Antibiotic	**Interpretation**
amikacin	S
cefoxitin	I
ciprofloxacin	S
clarithromycin	R
sulfamethoxazole/ trimethoprim	S
doxycycline	R
imipenem	I
moxifloxacin	S
tobramycin	S

Table 2. *M. abscessus* susceptibility report

Mycobacterium abscessus subsp bolletii. (erm41 gene: not detected)		
Antimicrobial (MIC "S" range, mcg/ml)	**MIC, mcg/ml**	**Interpretation**
amikacin (1-64)	16	S
cefoxitin (4-128)	32	I
ciprofloxacin (0.12-4)	>4	R
clarithromycin (0.06-16)	0.5	S
imipenem (2-64)	16	I
linezolid (1-32)	32	R
doxycycline (0.12-16)	>16	R
sulfamethoxazole/ trimethoprim (0.25/4.75-75.8/152)	8/152	R
tobramycin (1-16)	16	R
moxifloxacin (0.25-8)	>8	R

Contact Information

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